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CASE REPORT

Survival and Vision Restoration Following Severe Metformin-associated Metabolic Acidosis With Transient Blindness: A Case Report and Review of the Literature

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Abstract

Metformin-associated lactic acidosis (MALA) is a life-threatening condition that may occur as a side effect of biguanides. This condition has a mortality rate of approximately 55 % depending on the severity. Typical symptoms include abdominal pain, nausea, vomiting, and diarrhea, but may also manifest with severe symptoms such as blindness, distributive shock, and renal failure requiring ICU level care. We present the case of a female in her early 70s who arrived at the emergency department with altered mental status and new-onset blindness, later diagnosed with severe acidosis (pH 6.607). She was intubated for hemodynamic instability and continuous renal replacement therapy (CRRT) was started to address her acid-base status. Her metformin concentration was found to be exceptionally high at 34 mcg/ml, significantly surpassing the normal range of 1−2 mcg/ml. Fortunately, the patient survived and was subsequently transferred to the medical floors in stable condition. Physicians should perform medication review and consider "MALA" as a potential etiology of severe acidosis when forming a differential diagnosis.

Keywords: Metformin, Lactic acidosis, Sepsis, Crrt

1. Introduction

Metabolic acidosis is a clinical disturbance defined by a pH less than 7.35 and a low HCO3 level.[1] Common causes of acidosis include toxic ingestion, ketoacidosis, renal failure, and lactic acidosis. While lactic acidosis is often attributed to tissue hypoxia, another rare and dangerous cause is MALA. Metformin, a commonly prescribed biguanide, exerts favorable effects on glucose metabolism in the treatment of patients with diabetes. MALA, however, presents a grave consequence of metformin accumulation carrying a mortality rate greater than 55 %. Due to challenges in diagnosis and management, it requires a high degree of suspicion and should be considered within the differential diagnosis in a patient presenting with pH less than 7.2. We present the case of a 72-year-old female who presented with encephalopathy, severe lactic acidosis on metabolic panels and blood gas analysis, and acute blindness that subsequently resolved following appropriate treatment.

2. Case presentation

A 72-year-old Caucasian female presented to the hospital via ambulance after her daughter found her to be encephalopathic and dysarthric. Her last known well was the night before. Her past medical history was significant for obesity, chronic kidney disease (CKD) stage 3, abdominal aortic aneurysm (AAA), type 2 diabetes mellitus, hypertension, dyslipidemia, osteoarthritis, hypovitaminosis D and

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NSAID use. Her home medications included metformin, allopurinol, aspirin, metoprolol, simvastatin, omeprazole, vitamin B-12 injections, vitamin D3, as well as NSAIDS for osteoarthritis pain, although the dosage and frequency were not clearly documented. On initial assessment, her initial vitals included a blood pressure of 80/42 mmHg, respiratory rate of 24 breaths per minute, heart rate of 103 beats per minute, and an oxygen saturation (SpO 2) of 90 % on 2L of oxygen via nasal cannula. Her temperature was 30.5 C. Physical examination was significant for bilateral vision loss, mild dysarthria, and upward gaze deviation. Computed tomography (CT) scans of her head revealed no acute processes. An electrocardiogram (EKG) was obtained and revealed an ectopic atrial rhythm with frequent premature ventricular contractions (PVCs). She was emergently intubated for airway protection in view of her encephalopathy and consequent impending respiratory failure.

Initial labs were significant for leukocytosis, an elevated anion gap, severe lactic acidosis, and elevated creatinine (see Table 1 for a summary of laboratory studies). Her serum metformin level was 34 mcg/mL. Urinalysis was positive for ketonuria (40), bacteriuria (1+/hpf), pyuria (>100 white blood cells/hpf), and moderate leukocyte esterase. A urine organic acid panel was also ordered, the results of which are found in Table 2. Arterial blood gasses (ABGs) were obtained after intubation and revealed a critically low pH of 6.607, partial pressure of carbon dioxide (pCO2) of 13.4 mmHg, partial pressure of oxygen (pO2) of 165.8 mmHg, and a bicarbonate (HCO3) of 1.3 mmol/L. Her blood pressure did not respond to fluid resuscitation, therefore she was started on a norepinephrine continuous infusion. She was administered sodium bicarbonate IV pushes and infusion. According to sepsis protocol broad antimicrobial coverage with vancomycin, cefepime, and metronidazole were initiated. She was transferred to the intensive care unit (ICU) for further management.

Table 1. Abnormal initial laboratory findings.

Abnormal Initial Labs	
WBC (K/mcL)	24.21
Hgb (g/dL)	11
MCV (fL)	108.5
Lactic Acid (mmol/L)	20.1
Anion Gap (nmol/L)	47
Sodium (mmol/L)	149
Potassium (mmol/L)	7.6
Bicarbonate (mmol/L)	2
Glucose Level (mg/dL)	131
BUN (mg/dL)	87
Creatinine (mg/dL)	8.4
ALT (units/L)	62
AST (units/L)	22
eGFR (mL/min/1.73m2)	4.3
Beta-hydroxybutyrate (mg/dL)	>46.0
Serum osmolality (mOsm/kg)	363
B-type Natriuretic Peptide (pg/mL)	15,502
High Sensitivity Troponin T (ng/L)	155
Ammonia Level (ug/dL)	516
Lipase Level (unit/L)	299

Table 2. Urine organic acid panel. We see a massive excretion of 3-OH-butyric and acetoacetic acids, with elevated branched-chain keto acids and severe lactic/pyruvic aciduria suggesting a severe catabolic state. The elevated excretion of adipic acid is most likely dietary in origin. Increased excretion of 4-OH-phenyllactic/phenylpyruvic acids suggests impaired hepatocellular function (OH) = hydroxy.

Urine Organic Acid Panel		
Organic acid	Level (mmol/mol creatinine)	Normal range
3-OH-Butyric Acid	12,288	0–4
Lactic Acid	5547	0–50
Acetoacetic Acid	4316	0–4
Adipic Acid	274	0–35
4-OH-Phenyllactic Acid	59	0–4
2-Keto-3-Methylvaleric Acid	32	0–10
2-Keto-Isovaleric Acid	29	0–4
Fumaric Acid	27	0–4
2-Keto-Isocaproic Acid	26	0–4
4-OH-Phenylpyruvic Acid	5	0–2
Ethylmalonic Acid	5	0–4
Suberic Acid	5	0–3

3. Clinical course

CRRT was provided to address her acute renal failure and severe metabolic acidosis. In the following hours, vasopressin, dopamine, and phenylephrine, as well as hydrocortisone and fludrocortisone were added to maintain a mean arterial pressure (MAP) above 65. An echocardiogram revealed an ejection fraction (EF) of 70–75 %, mild left ventricular hypertrophy, as well as moderately increased left atrial size. Sputum and nasal swab cultures were positive for methicillin-sensitive staphylococcus aureus (MSSA), while blood and urine cultures were negative leading to antimicrobial de-escalation to cefepime for 7 days.

As her acidosis improved, she was weaned off all pressor support and sedation. CRRT was discontinued on day five, and she was safely extubated. Her mentation improved and she reported a return of her vision. After eight days in the ICU, she was transferred to the general ward and eventually discharged on day 22 in stable condition.

4. Outcome and follow up

Her metformin was discontinued on hospital discharge and she was started on long-acting insulin

for the management of her diabetes. At her 1-month follow-up, she continued to be in relatively good health without recurrence of her symptoms.

5. Discussion

Metformin is a widely prescribed pharmaceutical agent utilized for the management of diabetes mellitus. This biguanide exhibits multiple benefits on glucose metabolism, such as the suppression of hepatic gluconeogenesis, the attenuation of fatty acid oxidation, and the augmentation of peripheral insulin-mediated glucose uptake.[2] While metformin is generally well tolerated, about 20−30 % of patients may experience side effects including nausea, vomiting, diarrhea, abdominal bloating, and anorexia - likely explained by the elevated concentration of metformin within the intestinal enterocytes.[3]

Another rare but noteworthy side effect of metformin use is the accumulation of lactic acid. Lactic acidosis, a metabolic disturbance characterized by elevated levels of lactic acid, can be classified into two types (A and B). Type A is primarily attributed to conditions that cause tissue hypoxia such as shock or severe anemia. Conversely, Type B is unrelated to tissue hypoperfusion and may result from factors including liver failure (resulting in impaired clearance), or the administration of certain drugs such as salicylates, antiretroviral medications and metformin. MALA is a dangerous condition that alters the normal gluconeogenesis process. By inhibition of the first step of gluconeogenesis, the conversion of pyruvate to oxaloacetate through pyruvate carboxylase, excess pyruvate gets converted to lactate and accumulates in the blood.[2]

Currently, MALA is estimated to affect approximately 4.3 per 100,000 patient-years.[4] It accounts for about 0.84 % of ICU admissions and is associated with a 30%−55 % mortality rate depending on severity.[5] Elevated levels of lactic acid have been extensively linked to a reduction of cardiac contractility, diminished responsiveness to vasopressors and, ultimately, the development of shock and death. Severe metabolic acidosis resulting from lactic acidosis has also been associated with the occurrence of transient blindness. Studies conducted on animal models have attributed this adverse event to the impairment of retinal cell function, which is directly influenced by pH. In mammalian organisms, retinal cell function becomes disrupted when the pH drops below 7.09.[6] In the case of our patient she had a pH of 6.607, likely leading to the interruption of signal transmission to visual neurons.

Table 3. Comparison of 7 published case reports of MALA.

Patient factors	Deepak et al. 2009[8]	Sendil et al. 2020[9]	Umeda et al. 2018[10]	Rai et al. 2020[11]	Santoli et al. 2023[12]	Watson et al. 2016[13]	Mikhail et al. 2023
Age	51	63	54	77	62	82	70
Sex	female	male	female	male	male	male	female
Clinical Presentation	Encephalopathy, Abdominal pain	Cardiac arrest	gastroenteritis	Abdominal pain, nausea, vomiting	Abdominal pain, nausea, vomiting	Nausea and vomiting	Encephalopathy
Metformin dosage	1000 mg BID	1000 mg BID	1000 mg BID	1000 mg BID	1000 mg BID	unknown	1000 mg BID
pH level	6.64	6.69	6.57	6.94	6.9	6.5	6.607
Bicarbonate level (mmol/L)	<5	4.8	2	8	5	unknown	2
Creatinine level (mg/dl)	7.4	15.95	8.07	7.39	13.3	unknown	8.4
Lactic acidosis (mmol/L)	23.8	12	16.3	13.1	11.7	28.6	20.1
Metformin level (mcg/ml)	unknown	29	42	23	unknown	unknown	35
Treatment	CRRT	CRRT	CRRT	CRRT	CRRT	CRRT	CRRT

Various factors could have contributed to the development of MALA in our patient, including sepsis secondary to a urinary tract infection (UTI), which subsequently led to a deterioration in renal function, particularly within the context of chronic kidney disease. This renal dysfunction heightened the patient's susceptibility to metformin accumulation due to compromised clearance, ultimately resulting in the exacerbation of acidosis. Notably, the patient had no history of other lactic acidosis-inducing drugs. Due to high clinical suspicion, serum metformin levels were measured and found to be 34 mcg/ml, well above the therapeutic plasma concentrations of 1–2 mcg/ml.

Upon literature review, cases of MALA with a pH < 7.0 at presentation were analyzed for similarities. Table 3 compares seven cases (including this one) and outlines the patient demographics, comorbidities, presentation, and interventions. Key similarities included a metformin dose of 1000 mg twice a day, as well as severe renal dysfunction requiring CRRT. One distinctive aspect of our case lies in the utilization of the diagnostic test known as urine organic acids. This test proved to be exceptionally informative, providing invaluable insights into the etiology of the patient's clinical condition. Given the overlapping clinical manifestations of septic shock and MALA, a high index of clinical suspicion is required to establish an accurate diagnosis and perform timely, life-saving interventions.

6. Conclusions

Severe acidosis carries a high mortality rate, often approaching and exceeding 55 % in patients with pH below 7.2.[7] MALA is increasingly recognized in patients using metformin with a predisposing clinical context, such as acute renal failure. We presented the case of a 72 year old female who developed sepsis from a urinary tract infection, developed acute renal failure, and severe lactic acidosis. This case highlights the importance of physicians being aware of the potential for metformin, a seemingly benign medication, to cause severe lactic acidosis and formulating a wide differential when encountering metabolic acidosis.

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Disclosures

None.

Conflict of interest

The authors have no conflicts of interest to disclose

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