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Case Report

Transient Blindness in Metformin-associated Lactic Acidosis: Resolution With Supportive Care

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Abstract

Metformin remains the first-line pharmacologic treatment for type 2 diabetes mellitus due to its well-established efficacy and safety profile. However, a rare but serious complication is metformin-associated lactic acidosis (MALA), which carries a mortality rate of up to 36.2% in hospitalized patients. Those with chronic kidney disease and cardiovascular comorbidities are particularly vulnerable to severe outcomes. Among the rare manifestations of MALA is complete bilateral blindness, which typically requires urgent hemodialysis for reversal. Here, we present a case of MALA-induced blindness that was unexpectedly reversed through supportive medical management alone, prior to hemodialysis. This case underscores the critical role of early recognition and intervention by intensive care physicians in optimizing MALA outcomes. Further studies are warranted to elucidate the effects of MALA on the visual pathways, particularly the susceptibility of retinal cells and photoreceptors to metformin toxicities.

Key Words: metformin, blindness, lactic acidosis, critical care

Introduction

Metformin is a glucose-lowering antidiabetic medication used as first-line therapy for type 2 diabetes mellitus (T2DM). It acts on various metabolic pathways within the gastrointestinal system and adipose tissues. Metformin primarily works by inhibiting hepatic gluconeogenesis, leading to complex changes in glucose metabolism, including the accumulation of lactic acid [1, 2]. In most patients, the accumulation of lactic acid at low levels is unlikely to cause clinically significant side effects. However, metformin-associated lactic acidosis (MALA) in patients with multiple comorbidities can result in detrimental metabolic derangements. The incidence of MALA ranges from 3 to 10 per 100 000 person-years and is linked to predisposing medical conditions such as acute and chronic kidney disease (CKD), congestive heart failure, and respiratory viral illnesses like COVID-19 [3-5]. These conditions heighten metabolic demand, increasing the risk of metabolic imbalances and electrolyte disturbances. Metformin inhibits the conversion of lactate into pyruvate, which, combined with increased metabolic demand, can lead to lactic acid buildup [6]. Furthermore, any concurrent acute or chronic kidney impairment during MALA is likely to affect the clearance of both lactic acid and metformin, exacerbating the accumulation of lactic acid itself [7].

Several retrospective studies across the United Kingdom, Taiwan, and Thailand report a mortality rate of up to 36.2% in patients hospitalized with MALA [8-12]. Key features associated with mortality include intentional metformin ingestion, admission to the intensive care unit with a high Acute Physiology and Chronic Health Evaluation II score, and stage 3 Kidney Disease Improving Global Outcomes acute kidney injury. These studies suggest that therapeutic doses in otherwise healthy patients with T2DM are unlikely to result in MALA. However, critically ill patients with multiple comorbidities are at increased risk. Therefore, MALA should be suspected in critically ill patients on metformin who present with high anion gap metabolic acidosis (HAGMA) that is due to lactic acidosis and cannot be explained by alternative etiologies [9, 12-14]. Although metformin levels can support the diagnosis, their interpretation is complicated by the lack of established therapeutic ranges [15]. Symptoms of MALA, such as nausea, lethargy, confusion, diarrhea, shortness of breath, dizziness, and lightheadedness, are nonspecific, making a thorough medication history and laboratory investigations essential for diagnosis [16, 17].

Here, we present a unique case of MALA associated with bilateral transient blindness, a rare phenomenon in critical care settings. In contrast to previously reported cases, this patient experienced a complete resolution of blindness with supportive therapy alone prior to hemodialysis [9, 18, 19].

Case Presentation

A 62-year-old woman with a history of CKD stage IIIA and T2DM presented to the emergency department with a 3-day history of nausea, vomiting, diarrhea, and abdominal pain. Her diabetes regimen included metformin 1000 mg twice

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daily for the past 7 years, along with insulin glargine and insulin lispro, all of which were continued during her acute illness. Initial vital signs showed hypothermia, with a temperature of 33.7 degrees Celsius, and hypertension, with a systolic blood pressure of 191 mmHg and a diastolic blood pressure of 96 mmHg. Heart rate was 88 beats per minute, respiratory rate was 20 breaths per minute, and oxygen saturation was 98% on room air. Hypotension developed over 9 hours, reaching a nadir of systolic blood pressure of 74 mmHg and diastolic blood pressure of 47 mmHg.

Diagnostic Assessment

Laboratory investigations revealed HAGMA, with a pH < 7 (reference range, 7.31-7.41), venous pCO2 of 17 mmHg (reference range, 41-51 mmHg), lactic acid at 20.5 mmol/L (reference range, 0.5-2.2 mmol/L), bicarbonate < 2 mmol/L (reference range, 22-29 mmol/L), an anion gap of 48 mmol/L (reference range, 10-19 mmol/L), serum osmolality of 352 mOsm/kg (reference range, 275-295 mOsm/kg), glucose at 33 mg/dL (international system of units [SI]: 1.8 mmol/L) (reference range, 70-99 mg/dL [SI: 3.9-5.5 mmol/L]), and hemoglobin A1c of 7.5% (SI: 58.5 mmol/mol) (reference range, 4.0-5.6% [SI: 20.2-37.7 mmol/mol]). Additionally, serum chemistry revealed acute kidney injury with a creatinine of 13.52 mg/dL (SI: 1196 µmol/L) (baseline 1.0-1.2 mg/dL) (reference range, 0.5-1.04 mg/dL [SI: 88-106 µmol/L]), estimated glomerular filtration rate (eGFR) 3 mL/min/1.73 m^2 (baseline 50-60 mL/min/1.73 m^2) (reference range, ≥60 mL/min/1.73 m^2), and potassium level of 6.0 mmol/L (reference range, 3.5-5.3 mmol/L). The infectious work-up was positive for SARS-CoV-2, while the toxicology screen was negative for alcohol and glycols. While in the emergency department, the patient developed acute painless bilateral blindness. A neurology examination was remarkable for complete bilateral vision loss in all fields, with minimally reactive pupils and spontaneous ocular movement. Otherwise, the cranial nerve examination was normal, motor function was 5/5 in all muscle groups, and sensory function was intact. A computed tomography of the brain with stroke protocol showed no evidence of an acute intracranial process. A computed tomography angiogram of the brain and neck showed patent intracranial and cervical vasculature without high-grade stenosis, large vessel occlusion, or aneurysm.

Treatment

While receiving medical management with IV fluid resuscitation with crystalloids and sodium bicarbonate, the patient experienced a spontaneous return of vision 2 hours later, without any further neurological complications or deficits. Subsequently, the patient was admitted to the intensive care unit for pressor support and urgent hemodialysis.

Outcome and Follow-up

Repeat laboratory investigations following hemodialysis showed pH of 7.36, venous pCO2 of 22 mmHg, lactic acid of 10.5 mmol/L, bicarbonate of 12 mmol/L, anion gap of 36 mmol/L, creatinine of 6.56 mg/dL (SI: 579.9 µmol/L), eGFR of 7 mL/min/1.73 m^2, and potassium of 4.4 mmol/L. Follow-up magnetic resonance imaging 3 days later showed a chronic lacunar infarct in the left basal ganglia without signs of acute intracranial hemorrhage or infarction. Repeat chemistry at 1, 6, and 10 weeks showed persistent renal impairment with creatinine of 3.04 mg/dL (SI: 269 µmol/L), 1.29 mg/dL (SI: 114 µmol/L), 1.54 mg/dL (SI: 136 µmol/L) and eGFR of 17 mL/min/1.73 m^2, 47 mL/min/1.73 m^2, and 38 mL/min/1.73 m^2, respectively.

Discussion

MALA is a rare and life-threatening condition reported in T2DM patients worldwide. Complicating this presentation is the occurrence of transient blindness in a subset of patients without known ophthalmological disease. Previously published case reports of MALA with transient blindness required hemodialysis for complete resolution of this neurological deficit [9, 18, 19]. While the patient, in this case, underwent hemodialysis to correct the underlying metabolic derangements, a key distinguishing feature is the reversal of blindness achieved with IV fluid resuscitation using crystalloids and sodium bicarbonate alone, prior to the initiation of hemodialysis. This emphasizes the essential role of critical care physicians in recognizing this rare condition and initiating medical management pending definitive correction with hemodialysis. Additionally, this case illustrates the long-term impact of MALA on kidney function. Follow-up laboratory investigations for up to 10 weeks showed the progression of her underlying CKD, highlighting the need for vigilant monitoring and nephrology review.

MALA with transient blindness is an extremely rare condition with limited available literature. However, the development of transient blindness in MALA is likely multifactorial, relating to drug toxicity, hemodynamic instability, and metabolic and electrolyte derangements. T2DM is a well-known cause of retinopathy, and patients with diabetes experiencing blindness in MALA likely have an underlying level of diabetic retinopathy, which predisposes them to this condition. Moreover, a key potential mechanism is the disruption of acid-base physiology in the retina, which impairs photoreceptor transmission and leads to blindness [19-22]. Evidence supporting this hypothesis includes the reversal of blindness with crystalloids and sodium bicarbonate in our case and with hemodialysis in previously published case reports [9, 18, 19]. Transient blindness has also been reported in other cases of metabolic acidosis, including alcoholic and diabetic ketoacidosis [23, 24]. However, this phenomenon does not appear to occur in cases of respiratory acidosis, suggesting that the acid-base disturbance alone is insufficient to cause blindness and that other contributing substrates specific to metabolic acidosis, such as ketone bodies, potentially contribute to this presentation.

Hypotension is another common feature among patients experiencing MALA and transient blindness. This is likely a result of severe acidosis, which induces a systemic vasodilatory response. While brain imaging in our case did not reveal radiological evidence of acute ischemia, acute hypotension may lead to undetectable ischemia in the retina, occipital lobe, and optic nerve that impairs their function [25]. The painless and transient nature of this phenomenon aligns with a transient ischemic attack or amaurosis fugax [26]. However, its bilateral and uniform presentation without a history of cardiovascular or rheumatological disease makes this diagnosis less probable [26]. Additionally, hypoglycemia has been noted in a subset of MALA cases. In this patient, the diabetic regimen, which includes metformin and insulin, was continued during her acute illness. The continued use of these medications, particularly during an episode of acute illness, likely exacerbated her hypoglycemia, which may have further impaired the function of her visual pathways, including the retina.

While none of these etiologies may be solely responsible for transient blindness in MALA, collectively, they have a significant cumulative effect on visual pathways. Metabolic acidosis likely sensitizes retinal cells to ischemic damage in predisposed patients with diabetes, leading to blindness. Prompt critical care interventions to correct acid-base disturbances and manage hypotension are crucial for reversing this condition. We predict that delays in recognizing and treating this condition may lead to irreversible blindness and progression to include additional neurological deficits.

Learning Points

- It is crucial to maintain a high level of clinical suspicion for MALA in critically ill patients who use metformin and present with HAGMA, especially in those with acute or chronic renal impairment, cardiovascular compromise, or acute infections.
- Prompt medical management and fluid resuscitation can reverse blindness in a subset of patients with MALA while waiting for further correction of metabolic derangements through hemodialysis.
- Multidisciplinary and long-term outpatient follow-up is essential to optimize kidney function and ensure complete recovery of neurological deficits.

Contributors

All authors made individual contributions to authorship. Y.A., A.N., and M.I. were involved in the diagnosis and management of the patient and manuscript submission. All authors reviewed and approved the final draft.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from patient.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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