THE DARK SIDE OF BIGUANIDES: A CASE REPORT ON METFORMIN-ASSOCIATED LACTIC ACIDOSIS (MALA)

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Abstract

Metformin-associated lactic acidosis (MALA) is a rare but potentially fatal complication that can occur in a patient on metformin, who had a sudden reduction in the renal function resulting in a raised serum metformin level. We describe a case of MALA who survived with prompt haemodialysis. An elderly female with diabetes on metformin presented with gastrointestinal losses, lethargy and confusion. She was in circulatory shock and despite an aggressive fluid regime, she remained acidotic with an increasing lactate level of > 15 mmol/L. After endotracheal intubation, she was referred to tertiary centre for haemodialysis. Her serum lactate level rapidly fell to a satisfactory range and a progressive recovery followed. We are highlighting this case for its rarity and to serve as a guidance on the early recognition of MALA for fellow clinicians. Despite the high mortality rate, MALA is reversible, and we urge clinicians to expedite haemodialysis as definitive treatment.

Keywords: Metformin, Lactic Acidosis, Dehydration, Elderly

Introduction

Metformin is an oral hypoglycaemic agent (OHA) that belongs to a class known as biguanides. According to the Malaysian Clinical Practice Guideline 2021, metformin is recommended as the first-line OHA in patients with Type 2 Diabetes Mellitus (T2DM) without chronic renal impairment (1). Although largely safe to be used, one of its most fearsome complications is metformin-associated lactic acidosis (MALA). MALA is defined as 'an arterial pH 7.35 or less, and a lactate concentration of above 5 mmol/L in the setting of acute or chronic metformin exposure' (2). It is rare, with prevalence noted to be <10 cases per 100,000 patient-years of exposure (3). It is likely potentiated by dehydration and renal failure. The definitive treatment of MALA is haemodialysis to remove excessive serum metformin (4).

It is important for clinicians to consider the diagnosis of MALA when an elderly patient on metformin presents with high anion gap metabolic acidosis. We describe a case with such a classical presentation.

Case report

A 82-year-old female with underlying well-controlled hypertension and type 2 diabetes mellitus (T2DM) on tablet metformin 1 g twice daily and modified release tablet gliclazide 120 mg once daily, was brought in by family members due to generalized weakness and altered mental status. She experienced colicky abdominal pain, vomiting and loose stools more than 10 times with remarkably reduced oral intake over the past 2 days. They were also concerned as the patient appeared weak and stopped conversing with them. According to family members, the patient had joyously consumed large amounts of seasonal jackfruits and longans which she recently harvested from her own farm. They denied recent fever, cough, chest pain, shortness of breath, bleeding tendency nor dysuria. She did not drink uncooked water, swim in lakes nor engage in jungle trekking or experienced recent dog bite. She did not ingest any wild mushroom, toxins nor alcohol. She had no pre-existing renal impairment. She worked as a subsistence farmer and was physically fit. Family members emphasized that the patient has always been compliant to her metformin dose and confirmed that she took medication at regular times despite current illness. However, they were unable to verify if the patient had carelessly taken more metformin tablets than prescribed, considering patient's current confused state.

Upon arrival, the patient was in evident circulatory shock, with blood pressure 85/45mmHg, heart rate 56 beats per minute (bpm), tachypnoea with respiratory rate 24-26 per minute with intermittent Kussmaul breathing. Her temperature was 36.3^{o}C and her SpO2 was 96% under room air. Her serum glucose level was 11.3 mmol/L . Her peripherals were cool up to mid-arm and while she had spontaneous eye opening and movement, she was making only incomprehensible sounds. She appeared dehydrated with a coated tongue and dry skin turgor, lethargy and

was unable to sit up straight. Her heart and lungs sounds were normal and her abdomen was soft. There were no abnormal bruises, petechiae or rashes seen. She was catheterized but initially had no urine output.

The Sepsis 6 regime was immediately commenced with fluid resuscitation, oxygen supplement and empirical broad-spectrum antibiotics with intravenous ceftriaxone and metronidazole. Despite immediate normal saline boluses, she remained hypotensive and hence was started on low-dose inotropic support with noradrenaline. As the hydration continued, she appeared less lethargic and began answering questions but remained confused and not oriented to time, place, and person. Her serum biochemistry showed haemoglobin 12.6 g/dL, hyperleukocytosis with white cell count 19.65 x10^3/µL and borderline thrombocytopaenia 144 x10^3/µL. She also had acute renal injury with urea 17.4 mmol/L, creatinine 279 µmol/L with hyperkalaemia potassium 7.7 mmol/L and normal sodium level 134 mmol/L. She had no previous background of renal impairment. She also had transaminitis AST 369 U/L, ALT 325 U/L, mild hyperbilirubinemia and normal alkaline phosphatase. UFEME was clear urine without leukocytes nor ketone.

Her initial blood gas showed severe metabolic acidosis with pH 7.18 with bicarbonate 13.1, base excess -13.1, compensatory hypocarbia with hyperlactataemia (lactate 13.1 mmol/L). Contrary to clinical expectation, despite aggressive fluid resuscitation, although her peripherals became warmer up to wrist, she remained confused and oliguric. A total of 3 L normal saline was administered, and her urine output remained dismal just at tubing. She also developed an extreme bradycardia with heart rate at approximately 35 bpm. In spite of prompt resuscitation, her blood gas deteriorated to be as such: pH 6.97, bicarbonate 7.4, base excess -23.2 and lactate was now >15.0. As her anion gap was calculated to be 37, she was diagnosed with refractory, decompensated septic shock with high anion gap metabolic acidosis (HAGMA) secondary to metformin-associated lactic acidosis (MALA) in presumed acute gastroenteritis. Her INR was later revealed to be deranged at 2.3 and was diagnosed with acute liver failure. She was subsequently intubated for severe metabolic acidosis, mechanically ventilated then referred to tertiary centre for urgent hemodialysis and intensive care.

Once haemodialysis was performed, the patient's metabolic acidosis immediately resolved. Post-haemodialysis blood gas showed a pH 7.44 and bicarbonate 26.2 and lactate reduced to 3.1 then further progressed down-trends. She was also given N-acetylcysteine infusion for hepatic protection. As her recovery was satisfactory, she was extubated after 3 days and discharged from intensive care on Day 4. After a total of 2 weeks of hospitalization. She was able to resume her independent lifestyle at home.

Table 1: Blood investigation trend

	Emergency	ICU day 1	ICU day 2 (after dialysis)	Upon discharge
Total white cell count (10^3/µL)	19.65	29.3	26.25	9.9
Hemoglobin (g/dL)	12.6	11.4	11.9	9.1
Platelet (10^3/µL)	144	124	58	101
Sodium (mmol/L)	134	135	143	142
Potassium (mmol/L)	7.7	4.5	3.2	3.6
Urea (mmol/L)	17.4	18.49	9.91	4.9
Creatinine (µmol/L)	279	289	153	58
Aspartate transaminase (U/L)	369	4617	-	101
Alanine transaminase (U/L)	325	3595	4398	27
Alkaline phosphatase (U/L)	73	69	80	73
Albumin (g/L)	40	32	29	27
pH	7.18	7.26	7.44	-
Bicarbonate (mmol/L)	13.1	21.1	25.8	-
Lactate (mmol/L)	13.1	11.9	3.1	-
Activated partial thromboplastin time	29.1	-	31.6	-
Prothrombin time	19.7	-	26.4	-
International normalized ratio (INR)	1.73	-	2.32	-

Discussion

Metformin is recommended by the Malaysian Clinical Practice Guideline 2021 as the first-line oral hypoglycemic agent (1). It is known for its effect in lowering serum glucose level and to potentiate weight loss.

Although largely safe to be used, according to the Malaysian guideline, metformin should be withheld when the creatinine clearance is less than 30 ml/min. This is because biguanides are known to be renally excreted. When patients have renal impairment, metformin may

accumulate and potentially causes hypoglycaemia. Another most feared adverse effect of biguanide use is lactic acidosis. While it is rare, many case reports on MALA typically describe elderly patients. It is likely due to the elderly having lower levels of fluid and renal reserve, which leaves them vulnerable as they deteriorate rapidly in illness.

The pathophysiology of MALA is complex, but it is widely accepted that it occurs as metformin may halt the hepatic mitochondrial respiration, leading to lactataemia (5). Predisposing risk factors include old age, renal failure, dehydration, alcohol use and sepsis (2). As acute renal injury takes place, the metabolism and excretion of metformin decline, leading to the accumulation of serum metformin which induces hyperlactatemia and subsequently lactic acidosis (6). In MALA, the definitive treatment is hemodialysis to remove excessive serum metformin while correcting metabolic acidosis (4).

In our case report, while we are confident with the diagnosis of MALA, it is worthwhile to unveil the mystery of the aetiology of MALA. The key of promptly diagnosing MALA in our case was knowing that the patient had taken her usual metformin dose, and possibly more despite ailment. In such scenario, obtaining the therapeutic drug level of metformin and its monitoring would have been greatly beneficial in determining the level of the serum biguanide required to cause lactic acidosis. Unfortunately, a serum metformin level was not performed as this test is not available in Malaysia. On the other hand, we wonder if the patient's symptoms of gastrointestinal losses and weakness were due to MALA, or had precipitated MALA. It is believed that the clinical presentation of this patient's MALA was paradoxical and multifaceted, as large amounts of gastrointestinal losses had potentiated a rapid renal impairment leading to MALA, while the uncompensated hypovolemia had further compounded onto the severity of her lactatemia.

Several discussions have been carried out on whether the cause of such severe gastrointestinal losses can be due to more serious systemic infections as these can mimic MALA (5). In view of initial clinical evaluation with patient in evident circulatory collapse, we had administered broad-spectrum empirical antibiotics ceftriaxone and metronidazole to cover infections like anaerobic, gram-negative bacteremia or leptospirosis, which is endemic in Malaysia. Notably, the patient's blood cultures grew no organisms. Microagglutination test for leptospirosis was carried out and the final titre was revealed to be 1:100 which is unlikely to be an active infection. We speculate that, in the background of advanced age, the patient experienced a simple food poisoning after consuming the harvested fruits, which rapidly transpired when she became severely dehydrated. This caused the decreased renal excretion of the metformin residual in her body, which, along with the reduced oral intake, led to MALA. To reinforce this aspect, a serum metformin level would have been helpful in supporting this diagnosis.

Lastly, despite a mortality rate of 21-25%, MALA is reversible with prompt haemodialysis and judicious fluid and supportive care (3, 7). We urge all clinicians to consider the diagnosis of MALA as early detection is associated with a favourable outcome after haemodialysis.

Conclusion

Cohort studies and prospective trials have been published extensively on Cochrane review stating that there is no evidence of metformin increasing the risk of lactic acidosis. However, scenarios may differ in reality (8). It is vital for clinicians to understand that metformin is still the most prescribed OHA with a good safety profile in T2DM. Nonetheless, clinicians should follow the latest guideline when prescribing metformin and regularly monitor the patients to prevent this catastrophic complication.

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Consent

Verbal consent for anonymous case report was obtained from patient's caretaker and children. Patient was unable to come back for follow-up in our centre due to logistic issue and old age.

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None

Competing Interests

None

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