A Unique Case of Metformin-Associated Lactic Acidosis

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Case presentation

- An 82-year-old man who lived alone was brought to a regional hospital from his home after being found by his family in **a confused state**.

PMH

- His past medical history was significant for **DM2, hypertension, dyslipidemia, benign prostatic hyperplasia, and chronic back pain**.
- He had **no known** prior history of cardiac or renal disease, and baseline serum creatinine [Cr] was **79 μmol/L.**

DH

- metformin 1000 mg p.o. BID,
- sitagliptin 50 mg p.o. BID,
- ramipril 10 mg p.o. daily,
- tamsulosin 0.4 mg p.o. daily,
- hydrochlorothiazide 25 mg p.o. daily,
- and meloxicam 7.5 mg p.o. daily.

- On initial assessment, the patient was in no acute distress, although he was **disoriented and confused** (GCS:14)
- He complained of **mild nausea** with recent decreased oral intake, but there was no history of diarrhea. He had no history of infectious symptoms, toxic ingestions, recent medication changes, or witnessed seizure activity.

V/S

- On physical examination he had normal cardiorespiratory findings and no focal neurologic signs. His initial vital signs were blood pressure **150/83 mm Hg**, heart rate **124/min**, respiratory rate **33/min**, oxygen saturation **100%** on room air, and temperature **34.9° Celsius**.

Hb [g/L]	130 [140-180]
WBC [x10^9/L]	**17.3** [4.0 – 11.0]
Platelets [x10^9/L]	286 [150 – 400]
pH [Venous]	**6.85** [7.33 – 7.46]
pCO_2 [Venous] [mmHg]	**19.3** [40.0 – 50.0]
HCO_3^- [Venous] [mmol/L]	**3.4** [22.0 – 27.0]
Na^+ [mmol/L]	145 [135 – 145]
K^+ [mmol/L]	**8.3** [3.5 – 5.1]
Cl^- [mmol/L]	101 [100 – 110]
Anion Gap [mmol/L]	**40.6** [5 – 12]
Albumin [g/L]	28 [34 – 46]
Glucose [mmol/L]	**1.4** [4.0 – 11.0]
Creatinine [μmol/L]	**967** [58 – 110]
Urea [mmol/L]	**31.2** [2.5 – 7.0]
PO_4^{-2} [mmol/L]	**3.68** [0.80 – 1.45]
Ca^{2+} [mmol/L]	2.43 [2.20 – 2.52]
Mg^{2+} [mmol/L]	0.84 [0.65 – 0.90]
Bilirubin [μmol/L]	6 [3 – 17]
ALT [Alanine Aminotransferase] [U/L]	22 [20 - 70]
AST [Aspartate Aminotransferase] [U/L]	32 [15 – 45]
ALP [Alkaline Phosphatase] [U/L]	44 [40 – 115]
aPTT [Activated Partial Thromboplastin Time] [s]	**45** [22-30]
PT [Prothrombin Time] [s]	**21.3** [10.1 – 14.6]
INR [International Normalized Ratio]	**1.9** [0.9 – 1.2]
Lipase [U/L]	351 [45 – 300]
Lactate [mmol/L]	**14.9** [0.5 – 2.2]
CK [Creatinine Kinase] [U/L]	65 [30 – 200]
Troponin I [ng/L]	32 [<30]

- A chest X-ray was unremarkable,
- Electrocardiogram showed a wide QRS complex, prolonged PR interval, and peaked T waves.

- He was initially treated with **intravenous [i.v.] dextrose**, a **crystalloid bolus**, and **calcium gluconate**, and his potassium was shifted intracellularly with **inhaled salbutamol and i.v insulin**. He also received one **ampule of i.v. sodium bicarbonate**

- Given his profound metabolic disturbances, He was urgently transferred by ambulance to the local tertiary care centre for expedited management and consideration of dialysis.

- Upon arrival to the Emergency Department of the tertiary care hospital, he was oriented to person and place **but not time**
- Vital signs were: blood pressure **110/80 mm Hg**, heart rate **80/min**, respiratory rate **20/min**, and oxygen saturation **100%** on room air.

- Within 30 minutes of arrival his **mean arterial pressure [MAP] dropped to <65 mm Hg**, and he required norepinephrine and vasopressin infusions as well as consultation with the intensive care unit [ICU]. At this time he also received a bolus of 1.5 litres of normal saline, and his axillary temperature was measured as **32.1° Celsius**

pH [Arterial]	**<6.75** [7.38 – 7.46]
pCO_2 [Arterial] [mmHg]	**<12** [32 – 45]
HCO_3^- [Arterial] [mmol/L]	**"No result"** [22 - 27]
Lactate [mmol/L]	**16.0** [0.5 – 2.5]
Na^+ [mmol/L]	142 [136 – 145]
K^+ [mmol/L]	**5.6** [3.5 – 5.1]
Cl^- [mmol/L]	107 [98 – 107]
Anion Gap [mmol/L]	**31** [5 – 12]
Glucose [mmol/L]	13.7 [4.0 – 11.0]
Creatinine [μmol/L]	**794** [49 – 93]
Urea [mmol/L]	**33.0** [2.1 – 8.0]

- Blood cultures and serum toxicology screen for ethanol, methanol, isopropanol, acetone, ethylene glycol, acetaminophen, salicylates, and tricyclic antidepressants were negative.

- His remaining metabolic workup, including plasma TSH and plasma cortisol, was normal. Computerized tomography of the head, abdomen, and pelvis were negative for acute findings with no evidence of urinary obstruction or hydronephrosis.

- The patient's level of consciousness remained stable, and he consistently protected his airway.
- He required infusion of vasoactive agents for approximately 20 hours to maintain adequate blood pressure.
- He was heated externally using warming blankets

- His urine output during the first 24 hours of admission was 205 mL.
- In addition to treatment with i.v. crystalloid and bicarbonate, he underwent urgent hemodialysis treatment [dialysate HCO_3^- concentration of 36 mEq/L] via central venous access, which was repeated the next day.

- After two days he was transferred out of the ICU and went on to achieve renal recovery [serum **Cr 95 μmol/L** on day 8 of hospitalization] with restoration of urine output, acid-base and electrolyte balance. His functional status at the time of discharge was at his baseline.

- The metformin was discontinued from the day of admission, and he was prescribed a new regimen of oral antihyperglycemic medications for his diabetes.

Metformin

- Medication of the **biguanide** class
- Commonly used first line oral agent for the treatment of type II diabetes mellitus [DM2]
- Mechanisms: an increase in peripheral insulin sensitivity, improvement in peripheral glucose uptake, and a decrease in hepatic gluconeogenesis
- Primarily excreted in the urine
- Dose adjustments are recommended for estimated **GFR:45 mL/minute/1.73 m^2 or less**.
- Common adverse effects :gastrointestinal complaints, including nausea, bloating, and diarrhea [6].

MALA

- The rarest and **most dangerous complication**
- The incidence of MALA in patients without renal disease is low, with a reported estimate of 5 cases per 100,000 patient-years
- The pathophysiology of MALA is thought to be multifactorial in nature. In rat models, metformin has been shown to promote lactate production in enterocytes
- Additionally, given that lactate is one of the substrates for hepatic gluconeogenesis, an accumulation of lactate may occur when this process is inhibited by metformin

- A separate retrospective study, involving 42 patients admitted to the intensive care unit, concluded that MALA related to intentional metformin overdose portends a much more favorable prognosis compared with MALA related to incidental metformin accumulation with concurrent medical illness
- Higher mortality was associated with increased age, lower arterial pH, elevated prothrombin time, and need for mechanical ventilation and vasoactive medications.

- mortality rates for MALA: case series of 49 patients with MALA reported an overall mortality rate of 45%
- The same study found that the degree of serum lactate elevation and serum metformin concentration **do not appear** to play prognostic roles.

Discussion

- This patient presented with **acute kidney injury** associated with severe **hyperkalemia, hypoglycemia**, and a profound **metabolic acidemia** with **elevated anion gap and serum lactate levels.**

- The patient's high anion gap metabolic acidosis was **likely due to lactic acidosis and acute kidney injury**, and he demonstrated appropriate respiratory compensation.
- Despite having severely depressed pH and HCO_3^- levels however, the patient maintained consciousness throughout and did not require ventilatory support.

- Although a serum metformin assay was not available at our institution, other causes of elevated serum lactate including sepsis and tissue ischemia were ruled out, and there was no evidence of hepatic disease or toxic ingestions.

- Although the patient's transient hypotension may have contributed to his lactic acidosis, his serum lactate was significantly elevated on initial presentation, prior to the requirement of vasoactive agents. Overall, his presentation was in keeping with MALA.

- In this case, it is unclear what precipitated the patient's rapid decline and initial presentation to hospital, as history was limited.
- However, based on his medication profile and laboratory findings, it is possible that he developed acute kidney injury secondary to extracellular volume contraction in the setting of nonsteroidal anti-inflammatory [meloxicam] and ACE inhibitor [ramipril] use, with resultant hypoglycemia and severe lactic acidosis secondary to metformin accumulation.

- Thus, this case illustrates the potential danger of volume contraction in elderly patients with DM2 who are treated with renin-angiotensin blockade, nonsteroidal anti-inflammatories and metformin, which can set off a cascade of events leading to life-threatening MALA.

- This case was unique for several other reasons.
- Firstly, the patient's initial clinical appearance and findings on exam were not suggestive of critical illness, and very much out of keeping with his abnormal biochemical profile.

- Despite having undetectably low serum pH and bicarbonate values, he was able to maintain an acceptable level of mentation, and consistently protected his airway without the need for intubation.
- In this regard, a correlation exists between low pH and altered mental status, with progression to coma frequently seen in patients with serum pH <6.9

- Hypothermia in MALA has been described previously in several case reports
- Hypothermia in cases of severe MALA may be a consequence of systemic vasodilation, which is induced by acidemia .

- Hypoglycemia is also known to cause hypothermia as a result of decreased available substrate for cellular respiration and heat production. In our patient, the combination of **acidemia** and **hypoglycemia** can explain his significant hypothermia, given that central, infectious, traumatic, and other endocrine causes of hypothermia were ruled out.

- The patient's coagulopathy on presentation cannot be explained by liver disease, clotting factor deficiencies, or recent use of anticoagulant medications. It is possible that he may have developed vitamin K deficiency given his history of decreased oral intake.

- However, his INR and PTT corrected within 12 hours of admission, which is sooner than expected for reversal of a vitamin K deficiency. Therefore, it is most likely that our patient developed a coagulopathy as a result of the combined effects of **hypothermia and acidemia**, which corrected shortly after **warming** and treatment with **bicarbonate and hemodialysis**.

- Finally, an interesting aspect of this case was the result of the ABG The arterial pH and bicarbonate were reported as **“<6.75” and “No result”**, respectively.
- These values reflect the fact that the patient's true serum pH and bicarbonate were below the detectable limit for our institution's blood gas analyser.

conclusion

- This case demonstrates the importance of early recognition of MALA in patients taking metformin who **present with an unexplained high anion gap metabolic acidosis with elevated lactate levels**.
- Such patients may present with clinical findings that do not correlate with their metabolic derangements and are at risk of rapid deterioration.

- Despite his advanced age and severe metabolic derangements, our patient had a very favorable outcome, perhaps as a result of prompt medical intervention, coupled with his relatively few medical comorbidities.
- Additionally, this case highlights the need for healthcare providers to educate patients about the importance of temporarily discontinuing metformin and other potentially nephrotoxic medications in the settings of acute illness and extracellular volume contraction.