Hong Kong College of Physicians
Case Report for Interim Assessment
Specialty Board of Advanced Internal Medicine (AIM)

For AIM Training, case reports should be submitted in the prescribed format together with the application form for Interim Assessment at least EIGHT Weeks before the date of Interim Assessment

Name of candidate (print and sign): Ng Chin Ting Justin
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Name of supervisor (print and sign): Professor Lau Kui Kai Gary
Date(s) and place (hospital) of patient encounter: June 2024 Queen Mary Hospital
Date of report submission: September 2024

Case report

Note: Failure to follow the prescribed format (including the number of words) results in a FAILURE mark (score between 0 and 4) for the Case Report.

Title: Metformin associated lactic acidosis. To fear or not to fear.

Case history:

We encountered Mr Chan, a 71-year-old man who could walk unaided and had a past medical history of hypertension, hyperlipidaemia, type 2 diabetes, lacunar stroke, and chronic kidney disease eGFR 70-80 (stage 2 chronic kidney disease). His medications included: aspirin, amlodipine, lisinopril, famotidine, and metformin.

He had just been discharged from the urology wards a few days ago following a brief admission for acute retention of urine, where he was successfully weaned off his urinary catheter and was discharged home with antibiotics and terazosin.

This time he presented to the emergency department with non-vertigo dizziness, vomiting & diarrhoea, and was found to have a low blood pressure of 90/40 and a low blood sugar of 2.9mmol/L. His Glasgow coma scale, GCS, was full at 15/15. He had no fever, his abdomen was soft, and

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a rectal examination revealed green stool. He was fluid resuscitated and given intravenous dextrose before being admitted onto the general medical ward.

Shortly after arriving onto the medical ward, he suffered an acute drop in his consciousness to a GCS of 8/15. His eyes were shut and he was no longer able to communicate, only screaming incomprehensible sounds. There was no obvious gaze deviation, pupillary disturbance, or lateralising weakness, and his plantar reflexes were down going bilaterally. Fortunately, at this time his vital signs were still stable. With such an acute change in his condition, we were limited to point of care bedside tests. His blood sugar level returned normal at 9.6mmol/L, however his arterial blood gas showed a very severe metabolic acidosis with a pH of 6.79, pCO2 of <1.7kPa, bicarbonate of 1mmol/L, and a base excess of -32mmol/L [Fig 1]. He was rushed into the intensive care unit where his blood pressure began to drop, requiring inotropic support.

He proceeded to have a CT brain, as well as a CT abdomen and pelvis. Both were unremarkable, with a CT brain only showing his previous lacunar infarct, and the CT abdomen and pelvis only showing fatty liver, with no evidence of ischaemic bowel or urinary obstruction. His bloods would later return showing a very high lactate of 26mmol/L, a severe acute kidney injury with a creatinine of 836μmol/L, and a very high ammonia of 415μmmol/L. His liver function was normal. A urine toxicology was also unremarkable.

A diagnosis of metformin associated lactic acidosis, MALA, was made and he was promptly started on haemodialysis. His condition dramatically improved with fluid resuscitation and haemodialysis. His lactic acidosis and ammonia resolved and his kidneys made a full recovery back to his previous baseline level. He was later stepped down onto the endocrine ward, where his metformin was resumed at a lower dose of 500mg twice daily. He was also newly started on insulin before being discharged home directly.

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Discussion and literature review

Metformin associated lactic acidosis, MALA, is a diabetic emergency, with a high mortality of 30-50% [1]. As the name implies, it is related to metformin's (and other biguanide's) ability to cause a build of lactic acid and thereby a potentially fatal high anion gap metabolic acidosis. The mechanism behind this is complex, but is believed to involve metformin's inhibitory effect on the electron transport chain of the mitochondria in the liver and skeletal muscles, impairing the mitochondria's ability to remove lactate via gluconeogenesis [1]. Although uncertain, the close relation of the electron transport chain and the Kreb's cycle within the mitochondria, may also explain the increased ammonia seen in cases of MALA. Drug induced hyperammonia via interference of the Kreb's cycle is already an established complication of other medications, most notably anti-epileptic medications such as sodium valproate [2-3].

The above mechanisms do not occur in most patients, and MALA usually takes place when there is an imbalance, with either a decreased ability to metabolise lactate, or an increased production of lactate. Decreased lactate metabolism either occurs directly due to impaired liver function, or in the setting of renal failure due to impaired excretion of metformin and thereby increased toxicity and lactate build-up via the mechanisms mentioned above. Increased production of lactate on the other hand, occurs in the setting of poor oxygenation and perfusion, as can occur in hypoxia, dehydration, sepsis, and heart failure. [1]

Even when the above does occur, MALA is still fortunately rare, with an incidence of <10/100,000, and therefore metformin is usually a very safe medication. On the other hand, Metformin also confers multiple benefits beyond simply lowering blood glucose. These include improved cardiovascular outcomes, weight neutrality, low hypoglycaemic risk, as well as cost effectiveness, making metformin still the first line choice for most patients with type 2 diabetes [1][4].

In fact, in 2016 the FDA revised its guidelines and restrictions on metformin use in chronic kidney disease, lowering the cut off eGFR to the current recommendation of 30ml/min/1.73m^2 [5].

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The latest consensus report in 2022 by the American Diabetic Association (ADA) and the Kidney Disease Improving Global Outcomes (KDIGO) echo this recommendation, and also advised reducing the maximum dose of metformin to 1g daily in patients with an eGFR of 30-44 ml/min/1.73m^2 or in patients with an eGFR of 45-60ml/min/1.73m^2 who have risks factors for lactic acidosis [4].

A recent retrospective cohort study in Hong Kong suggested that the limit for metformin use in chronic kidney disease could be pushed even lower, after it was found that patients who discontinued metformin once their eGFR decreased below 30ml/min/1.73m^2 actually experienced higher incidences of major adverse cardiovascular events, end stage renal failure, and death; with no increased incidence of lactic acidosis [6]. This suggests our current eGFR cut offs may be too cautious, and depriving our patients of optimal care. However, it should be noted that the average eGFR in both groups (patients who continued and discontinued metformin at eGFR <30) was 27ml/min/1.73m^2 i.e. only just below the guidelines recommended cut off of 30ml/min/1.73m^2. Therefore, while a lower eGFR cut off may achieve a better balance of metformin's benefit vs MALA risk, the optimal cut off may not be *that* much lower the current recommendations. Further studies are required to identify this optimal target eGFR.

Current guidelines recommend maintaining at least a minimum of annual monitoring of eGFR in diabetic patients taking metformin, increasing this frequency to every 3-6 month in patients with an eGFR <60 mL/min/1.73 m^2. The guidelines also suggest adopting sick days rules, and withholding metformin during acute illness, reflecting the observation that MALA is usually only found in the setting of acute illness and renal failure [4].

If preventative measures have failed, and the patient develops MALA, then its early recognition and appropriate treatment is important and has been associated with reduced morbidity and mortality [7]. A group in the Netherlands ambitiously looked for parameters that could be used in the Accident & Emergency setting to establish an early diagnosis of MALA and help differentiate it from sepsis. They found that lactate and creatinine were significantly higher in MALA cases compared with sepsis, and that pH and c-reactive protein levels were significantly lower. Within their small

cohort of patients, a combined raised lactate of 8.4mmol/L and a creatinine of 256μmol/L in a patient with metformin use, had a sensitivity of 85% and a specificity of 99% for diagnosing MALA [7]. While the small number of patients in their study limits the transferability of those absolute lactate and creatinine values, the general principles are still useful to aid an early diagnosis and expedite treatment, especially as the relatively specialist test of blood metformin level is not available in many clinical settings and its result may also not return in time [7-8].

There is no specific antidote for metformin toxicity in MALA and the treatment in mild cases is largely supportive, with haemodialysis used in more severe cases. Looking to provide more definitive guidelines, an expert panel The Extracorporeal Treatment in Poisoning Workgroup (EXTRIP) reviewed the existing literature and found lactate and pH were the most prominent markers of poor prognosis and therefore suggested the following indications for haemodialysis: lactate >20mmol/L or blood pH $\leq$ 7, with haemodialysis also to be considered when the lactate is >15-20mmol/L or pH 7.0-7.1, especially in the setting of shock, impaired kidney function, liver failure, or decreased consciousness [8].

The benefits of haemodialysis in the treatment of MALA are believed to extend beyond simply removing metformin, and include restoring acid base balance, removing lactate, correcting electrolyte disturbances, and also providing temporary renal support in cases where a worsening renal function may have contributed to the MALA [8].

In our case, Mr Chan's dramatic deterioration and recovery is testament to the severity of MALA and the importance of early haemodialysis in severe cases. His MALA was likely precipitated by a mixture of the acute renal failure and possibly a degree of urinary tract infection and sepsis following his acute retention of urine. His acute kidney injury was likely further exacerbated by the hypovolaemia caused by the vomiting and diarrhoea, which may in itself have also been a sign of metformin toxicity. Mr Chan's MALA may have been avoided with adequate monitoring of his renal function and appropriate sick day rules.

In conclusion, our case highlights the severe nature of this rare but important complication of one of the most commonly used medications in

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metformin. Judicious use of metformin and an awareness of when to reduce, withhold, and stop this medication is vital to avoiding its potentially lethal side effects, while benefiting from this clinically and cost-effective drug. Testing the limits to identify where the true optimal balance lies, will be the cautious task of future studies.

Tables and figures (where applicable) (no more than two figures)

Collect Date	09/06/24	09/06/24	09/06/24	09/06/24	**09/06/24**		
Collect Time	20:23	20:23	20:23	20:42	**20:54**		
Request No.	C6101035	C6101036	C6101041	C6101040	**C6090640**		
Remark	GE	GE	GE	GE	GE.Mask Type = Nasal Can.Flo...	Ref. Interval	Units
Comment					Below Nasal Can		
Mask Type					4.0		L/min
Flow Rate					40		%
% inspired O2					6.79 L	7.35 - 7.45	
pH					23.1 H	10.6 - 14.0	kPa
pO2					<1.7 L	4.7 - 6.0	kPa
pCO2					1 L	22 - 26	mmol/L
HCO3-					-32 L	(-4) - (+2)	mmol/L
Base excess							

Figure 1

Reference (not more than 10)

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2. Andrzejewski S, Gravel SP, Pollak M, St-Pierre J. Metformin directly acts on mitochondria to alter cellular bioenergetics. Cancer Metab. 2014 Aug 28;2:12
3. Upadhyay R, Bleck TP, Busl KM. Hyperammonemia: What Urea-lly Need to Know: Case Report of Severe Noncirrhotic Hyperammonemic Encephalopathy and Review of the Literature. Case Rep Med. 2016;2016:8512721. doi: 10.1155/2016/8512721. Epub 2016 Sep 21. PMID: 27738433; PMCID: PMC5050374.
4. de Boer IH, Khunti K, Sadusky T, Tuttle KR, Neumiller JJ, Rhee CM, Rosas SE, Rossing P, Bakris G. Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care. 2022 Dec 1;45(12):3075-3090.
5. The U.S. Food and Drug Administration (FDA). Drug Safety Communications: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function [Internet], 2016. Available from https://www.fda.gov/downloads/Drugs/DrugSafety/UCM494140.pdf. Accessed 10 Septemebr 2024
6. Yang A, Shi M, Wu H, Lau ES, Cheung JT, Zhang X, Fan B, Chen T, Kong AP, Luk AO, Ma RC, Chan JC, Chow E. Clinical outcomes following discontinuation of metformin in patients with type 2 diabetes and advanced chronic kidney disease in Hong Kong: a territory-wide, retrospective cohort and target trial emulation study. EClinicalMedicine. 2024 Mar 28;71:102568
7. van Berlo-van de Laar IRF, Gedik A, van 't Riet E, de Meijer A, Taxis K, Jansman FGA. Identifying patients with metformin associated lactic acidosis in the emergency department. Int J Clin Pharm. 2020 Oct;42(5):1286-1292. doi: 10.1007/s11096-020-01069-2. Epub 2020 Sep 22
8. Calello DP, Liu KD, Wiegand TJ, Roberts DM, Lavergne V, Gosselin S, Hoffman RS, Nolin TD, Ghannoum M; Extracorporeal Treatments in Poisoning Workgroup. Extracorporeal Treatment for Metformin Poisoning: Systematic Review and Recommendations From the Extracorporeal Treatments in Poisoning Workgroup. Crit Care Med.

2015 Aug;43(8):1716-30

No of words in Case History and Discussion (excluding references):___1592_____.

(should be between 1000-2000)

Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

(signature of Trainee)

Endorsed by Supervisor *

(signature of Supervisor)

* Supervisors must go over the Case Report with the Trainees, advise Trainees whether further amendments are necessary, review the Originality/ Similarity Report prepared by Trainees, adherence to the required format, sign on the report and remind Trainees on issues related to copyright and plagiarism.