CASE REPORT

Metformin-associated lactic acidosis mimicking ischaemic bowel

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SUMMARY

Metformin-associated lactic acidosis (MALA) is a rare complication among patients who are diabetic, commonly presenting with non-specific findings, and developing mostly among those with other risk factors for lactic acidosis. We report the development of MALA in a 67-year-old man with diabetes who presented with progressive abdominal pain and bloody diarrhoea. On presentation the patient was in shock, with signs suggestive of peritonitis, and with severe lactic acidosis, renal failure and non-specific findings on abdominal CT. Neither the patient nor family could provide details of his home pharmaceuticals. Circulatory resuscitation with intravenous crystalloids and vasopressors was commenced, along with empiric broad-spectrum antibiotics. Emergent laparotomy did not show pathological findings. Emergent haemodialysis, initiated postoperatively, resulted in rapid resolution of shock and lactic acidosis. A list of patient's medications, provided afterwards by the family, included metformin. Microbiological studies remained negative and renal function normalised by the time of patient's hospital discharge after 9 days.

BACKGROUND

Metformin is a commonly used antihyperglycaemic agent, employed as first-line therapy for type 2 diabetes, and is generally considered safe within prescribed use. However, lactic acidosis can develop among users, occurring rarely, with an estimated incidence of up to about 9 per 100 000 patient-years.[1] The complication, termed metformin-associated lactic acidosis (MALA), appears to develop predominantly among patients with renal failure, as kidneys are the primary route of metformin elimination, and often occurs in conjunction with other states associated with increased lactate production (eg, circulatory failure) and/or reduced lactate clearance (eg, hepatic dysfunction).[2]

Presenting manifestations of MALA are non-specific, often including lethargy, nausea, vomiting, abdominal pain and diarrhoea, with hypotension and hypothermia developing among the more severely ill. Serum levels of metformin are generally not available at clinical laboratories. The therapy of MALA is largely supportive, targeting specific organ dysfunction. In addition, haemodialysis is currently recommended, providing both rapid elimination of accumulated metformin and normalisation of the aberrant metabolic state, including lactic acidosis. Mortality among patients with MALA can be as high as 50%,[2] reflecting in part missed and delayed diagnoses.

We report the case of a patient with diabetes, with an initially unknown medication therapy, who presented with severe multiple organ failure, severe lactic acidosis and findings of acute abdomen suggestive of ischaemic bowel, prompting an emergent, but negative, exploratory laparotomy. A diagnosis of MALA was made following rapid clinical improvement with empirically initiated postoperative haemodialysis, and subsequent confirmation of patient's metformin use by family.

Our case highlights the many challenges faced by clinicians in timely diagnosis of MALA, especially when patients present with rare clinical manifestations, strongly suggestive of surgical emergencies.

CASE PRESENTATION

A 67-year-old Hispanic man presented to the emergency department (ED) with progressive diffuse abdominal pain and bloody diarrhoea for 5 days, unresponsive to ciprofloxacin therapy. He had history of type 2 diabetes mellitus, hypertension, ischaemic heart disease and hypothyroidism. The patient and family were unsure about remainder home medications.

On physical examination, Glasgow Coma Scale score was 12, temperature 96.5°F, blood pressure 70/38 mm Hg, pulse 63 beats/min, respiratory rate 38 breaths/min and oxygen saturation 94%, while receiving oxygen through nasal cannula at a rate of 6 L/min. The patient was in respiratory distress, with cold, clammy and mottled skin from his feet to mid-abdomen. There was abdominal guarding with rebound tenderness and bowel sounds were absent.

INVESTIGATIONS

Laboratory investigations showed serum anion gap 30 mmol/L; arterial pH 6.87; potassium 7.5 mmol/L; creatinine 13 mg/dL; blood glucose 137 mg/dL; and lactate 9.01 mmol/L; white cell count 23.8 ×10^9/L ; haemoglobin 10.9 g/dL; platelets 315 ×10^9/L ; bands 4%; Partial Thromboplastin Time 27.1 seconds; Prothrombin Time 17.4 seconds; and International Normalized Ratio 1.47. Urinalysis demonstrated no leucocytes. An assay for *Clostridium difficile* toxin by PCR was negative. CT of abdomen and pelvis was significant only for dilated bowel loops. Blood and urine cultures were obtained.

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DIFFERENTIAL DIAGNOSIS

- ischaemic bowel disease
- complicated acute gastroenteritis/colitis
- acute diverticulitis.

With septic shock resulting from any of the above.

TREATMENT

Initial circulatory resuscitation included intravenous crystalloids, norepinephrine and dopamine. Empiric antimicrobial therapy with piperacillin/tazobactam and vancomycin was initiated, and pharmacological treatment of hyperkalaemia was provided with intravenous insulin and dextrose, and with nebulised albuterol.

During the first 24 hours of hospitalisation, the patient was evaluated by an ED physician, medical residents, an intensive care specialist and two general surgery consultants. Due to the findings of an acute abdomen, the patient had an emergent exploratory laparotomy that was negative for any intra-abdominal pathology. The family was questioned again about patient's home medications and, specifically, use of metformin, as he was unable to communicate (being intubated and sedated), but use of metformin remained uncertain. Metformin level was not obtained, as this assay was not locally available.

A diagnosis of MALA was considered, despite lack of data on patient's home medications, given his diagnosis of diabetes, in the presence of severe acute renal failure and lactic acidosis, with negative surgical findings. Emergent haemodialysis was thus initiated. During haemodialysis patient's blood pressure improved significantly and vasopressors were discontinued after 18 hours. Serum lactate level decreased from 9.01 to 1.90 mmol/L after 24 hours. On the second hospital day a list of patient's home medications was brought by his daughter, and included metformin, glipizide, lisinopril, carvedilol, simvastatin and levothyroxine.

Microbiology studies remained negative. The combination of rapid resolution of shock and lactic acidosis with haemodialysis, in an at-risk patient with metformin exposure, who had unrevealing surgical exploration and negative additional work-up, supported a diagnosis of MALA.

OUTCOME AND FOLLOW-UP

No further haemodialysis was required following the initial session. There was no further diarrhoea, including after resolution of postoperative ileus, and the aetiology of its earlier bloody content remained unclear. The remainder hospital course was uneventful, with serum creatinine nearly normalised at the time of discharge, after 9 days of hospitalisation.

DISCUSSION

Blood lactate may be increased among metformin-treated patients, even when used as prescribed. This effect is thought to be related in part to inhibition of mitochondrial function, similar to other biguanides.[2] However, the increase in blood lactate with metformin therapy is generally minimal (mostly <1–2 mmol/L)[2] and, unlike other biguanides, lactic acidosis is rare, considered to be about 20 times less common than that with phenformin.[3]

The rarity of MALA remains unexplained, given the frequent occurrence of conditions predisposing to lactic acidosis (eg, sepsis and cardiac disease) and metformin accumulation (chronic and acute renal failure) among patients with diabetes. Indeed, MALA remains a rare complication, although it was estimated that about one in four metformin users have one or more contraindications to its use.[4]

The extent of diagnostic uncertainty faced by clinicians when considering MALA was demonstrated in a study by Stades and colleagues, who noted, on review of all identified reports of MALA, that 98% of eligible cases had one or more alternative risk factors for lactic acidosis.[5] More troubling was authors' report that there was not a single case among those reviewed where there was concurrence about a diagnosis of MALA among all reviewing experts.[5]

The combination of rare occurrence, non-specific presenting clinical findings, common concomitant presence of alternative causes of lactic acidosis and the noted disagreement about diagnosis even among experts deliberately considering possible MALA, may explain reported delayed or missed diagnosis.

Our case underscores the importance of clinicians' vigilance in pursuing data on possible metformin exposure among at-risk patients presenting with acute decompensation and lactic acidosis, and of considering the possibility of MALA even without conclusive exposure data, when findings are otherwise suggestive. However, as importantly, our patient's case highlights the additional challenges facing clinicians when addressing more rare manifestations of MALA, presenting with findings that traditionally require emergent, highly invasive interventions.

Our patient presented with typical findings of acute abdomen, suggestive of surgical emergency, likely acute ischaemic bowel, with concomitant life-threatening multiple organ failure. There have been, to our knowledge, only three metformin-treated patients reported to have clinical presentation suggestive of acute ischaemic bowel disease, in conjunction with acute renal failure and lactic acidosis.[6–8] All three had an unrevealing emergent abdominal exploration. Although, in contrast to our patient, use of metformin was known at time of presentation in all three, it appears that clinicians considered the possibility of MALA only after negative surgical exploration[6 8] and in one case only after patient's death.[7]

Although we cannot assume the initial therapeutic approach by involved clinicians, had patient's use of metformin been known at the outset, it is unlikely that the reported clinical findings would have been attributed exclusively to MALA at that time. This is because, broadly, patient's clinicians were faced with a choice, requiring an emergent intervention, between the possibility of a typical manifestation of a common problem (ie, acute abdomen due to a surgical emergency) and a rare manifestation of a rare condition (eg, acute abdomen due to MALA).

The present case suggests that while presenting findings strongly indicative of acute intra-abdominal surgical emergency may be rare among patients with MALA, patients' exposure

Learning points

- Metformin-associated lactic acidosis (MALA) may present rarely with findings strongly suggestive of an intra-abdominal surgical emergency, and surgical interventions may be unavoidable in some, even with known metformin exposure.
- Clinicians' vigilance is essential in ascertaining whether patients suspected to have MALA had metformin exposure; however, tentative diagnosis and haemodialysis may be required when other clinical findings are suggestive.
- Because patients with suspected MALA commonly have other potential causes of lactic acidosis, initial therapy has to be geared to address both possible MALA and other concurrent/alternative conditions, using specific interventions to address the latter.

to emergent, inherently risky, surgical interventions may be unavoidable in some. Nevertheless, our findings underscore the importance of clinicians' vigilance to ascertain pharmaceutical exposures of acutely ill patients.

Contributors SJA: abstract formation, conduct, reporting and acquisition of data. HL, LO: conception and design. NA: planning and design. ZH: literature review.

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