Case Report

Metformin-associated lactic acidosis and acute kidney injury in the era of COVID-19

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TABLE OF CONTENTS

1. Abstract

COVID-19, provoked by SARS-CoV-2, constitutes a global health issue with high rates of mortality. The presence of diabetes mellitus is associated with severe coronavirus COVID-19 as it is related to increased death rates in patients admitted to the intensive care unit. Acute kidney injury is a frequent complication among patients hospitalized for COVID-19 and is met with high morbidity and mortality. Here, we present a case of a diabetic patient with acute kidney injury, metformin-associated lactic acidosis, and COVID-19. Lactic acidosis is a relatively rare but noteworthy complication of metformin use. However, the combination of those life-threatening situations could prove fatal for the patients despite optimal medical care.

2. Introduction

Acute kidney injury (AKI) is a frequent complication among patients hospitalized for coronavirus disease COVID-19 and can rapidly progress to end-stage disease, or in some cases can be proved fatal and could be associated with in-hospital mortality. The incidence rate is high and some case series describe rates approaching 60% among hospitalized patients [1].

It is important to ask what we truly know about kidney involvement in COVID-19 and what still needs to be learned. In this case, the questions that should be answered are first, if patients who are taking metformin are more vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and if metabolic acidosis with AKI is in the majority of the cases a fatal condition.

3. Case presentation

A 70-year-old, nonsmoking woman with type II diabetes mellitus (T2DM) was transferred to the Emergency department (ED) with nausea, chest pain, and a 7-day history of diarrhea. Her past medical history included arterial hypertension and hypothyroidism. She had been taking metformin 1000 mg twice daily, a fixed combination of angiotensin II receptor blocker with a thiazide diuretic (olmesartan-hydrochlorothiazide), and levothyroxine 137 μg once daily.

Upon first medical contact, the patient appeared confused and not well-oriented. Her blood pressure was 150/90 mmHg, the oxygen saturation was 95% on room air, her heart rate was 150 beats per minute and she was afebrile. The clinical examination revealed a diffusely tender abdomen. The electrocardiogram showed supraventricular tachycardia with aberrancy.

The arterial blood gas (ABG) examination revealed a serious lactic acidosis. The pH was 6.71 and the HCO_3 levels were undetectable. The lactic acid was 15.7 mmol/L while the pCO_2 was 15 mmHg and the PO_2 was

94 mmHg. According to those findings paired with the history of metformin use, a diagnosis of metformin-associated lactic acidosis (MALA) was set.

Laboratory examinations revealed that her serum creatinine was 8.5 mg/dL, urea 237 mg/dL, potassium was 7 mEq/L while the C reactive protein was 0.9 mg/L (reference range <3 mg/L) (Table 1). The patient, however, had no history of pre-existing renal disease since serum creatinine and urinary protein-to-creatinine ratio were within the reference range 6 months before admission. Moreover, even though the chest X-ray was unremarkable, she was tested with a rapid antigen test for SARS-CoV-2 according to local protocols due to a low index of suspicion [lack of COVID-19-related symptoms (fever/cough/dyspnea), absence of abnormalities on chest imaging].

Table 1. Time course of laboratory and arterial blood gas parameters.

Laboratory parameter	Day 0	Day 1	Day 2	Reference range
WBC (K/μL)	17.36	13.8	8.87	4–10
Hemoglobin (g/dL)	8.5	8.3	8.2	11.8–17.8
Hematocrit (%)	28.5	25.6	24.2	37–47
Platelets (K/μL)	316	224	103	150–400
Glucose (mg/dL)	251	77	282	70–100
Sodium (mEq/L)	147	148	137	135–148
Potassium (mEq/L)	7	4.3	4.5	3.6–5.2
Urea (mg/dL)	237	124	119	15–50
Creatinine (mg/dL)	8.7	4.5	4	0.6–1
Total protein (g/dL)	7.2	6	5.9	6.4–8.2
Albumin (g/dL)	4	3.4	3.4	3.4–5
Magnesium (mg/dL)	2.4	1.6	1.8	1.6–2.4
Calcium (mg/dL)	10.2	9.2	9.2	8.5–10.1
Phosphate (mg/dL)	11	3.8	5.2	2.5–4.9
CRP (mg/L)	0.9	15.6	215	<3
hsTnI (ng/L)	54.6	2356	8992	<48
INR	1.17		1.45	0.8–1.2
D-dimers (μg/mL)	1.5			<0.5
Arterial Blood Gas analysis				
pH	6.71	7.28	7.29	7.35–7.45
pCO$_2$ (mmHg)	15	30	38	35–45
PO$_2$ (mmHg)	94	54	96	80–100
HCO$_3$ (mmol/L)	0	19	22	22–26
Lactate (mmol/L)	15.7	6	3	<2
Anion gap (mEq/L)	30	19	9	8–12

WBC, white blood cells; CRP, C reactive protein; hsTnI, high sensitivity troponin I; INR, international normalized ratio.

Due to the severity of her metabolic acidosis paired with the life-threatening hyperkalemia, she was given bicarbonate and calcium gluconate infusions. The rest of her in-hospital medical therapy consisted of normal saline (1 liter per day), levothyroxine (137 μg once daily), while she was initiated on long-actin insulin glargine (16 IU every evening, dose adjustment based on morning capillary glucose level) and bolus prandial insulin glulisine according to the clinic's "sliding scale" protocol.

The patient fulfilled the Extracorporeal Treatment in Poisoning (EXTRIP) Workgroup criteria for renal replacement therapy (RRT) initiation in metformin poisoning [2] and was transferred immediately to the hemodialysis (HD) unit. A temporal central venous hemodialysis catheter was placed and she underwent an HD session (Fig. 1). During the session, she developed hemodynamic instability requiring vasopressors. Consequently, the patient underwent a second hemodialysis session 6 hours later for the expected rebound of MALA due to metformin accumulation in peripheral tissues and erythrocytes [3].

During the 2nd day of hospitalization, she developed dyspnea of sudden onset with bilateral crackles and wheezing while the oxygen saturation had dropped to 80%. A repeat biochemical examination revealed leukocytosis and increased levels of inflammatory markers (C reactive protein: 215 mg/L, erythrocyte sedimentation rate: 103 mm/h).

Differential diagnosis included acute respiratory distress syndrome or acute pulmonary edema in the context of a new-onset respiratory infection. A chest and abdominal CT scan were ordered which demonstrated a small area of ground glass pattern at the right lower lobe. Even though the acidosis had largely improved (pH = 7.28), the ABGs revealed type I respiratory failure (PaO$_2$ <60 mmHg with low or normal PCO$_2$). An additional hemodialysis session was performed without clinical improvement and, consequently, she was intubated due to respiratory failure and upcoming respiratory muscle fatigue. Due to the growing suspicion for COVID-19 based on the rapidly deteriorating clinical course and the imaging findings, a polymerase chain reaction (PCR) of endotracheal aspirate sample for SARS-CoV-2 was ordered which turned positive. The patient was transferred to the COVID-19 unit and died the following day.

4. Discussion

COVID-19, provoked by SARS-CoV-2, constitutes a global health issue with high rates of mortality [4–6]. According to the World Health Organization COVID-19 dashboard, until 25 May 2021, there have been 167.011.807 confirmed cases of COVID-19, including 3.472.068 deaths. Cardiovascular disease and diabetes mellitus (DM) are associated with severe COVID-19 as they double the death rate and are increasingly prevalent in patients admitted to the intensive care unit [7, 8], with the upregulation of angiotensin converting enzyme-2 receptors in DM being a possible explanation for this interaction [9]. Adequate glycemic control is an additional critical factor influencing the prognosis of patients with DM and COVID-19 [10], who are already at an increased risk of ICU admission and death [11], since hyperglycemia, as detected in our patient at the day of admission, has been associated with poorer outcomes and a greater resistance to anti-interleukin-6 treat-
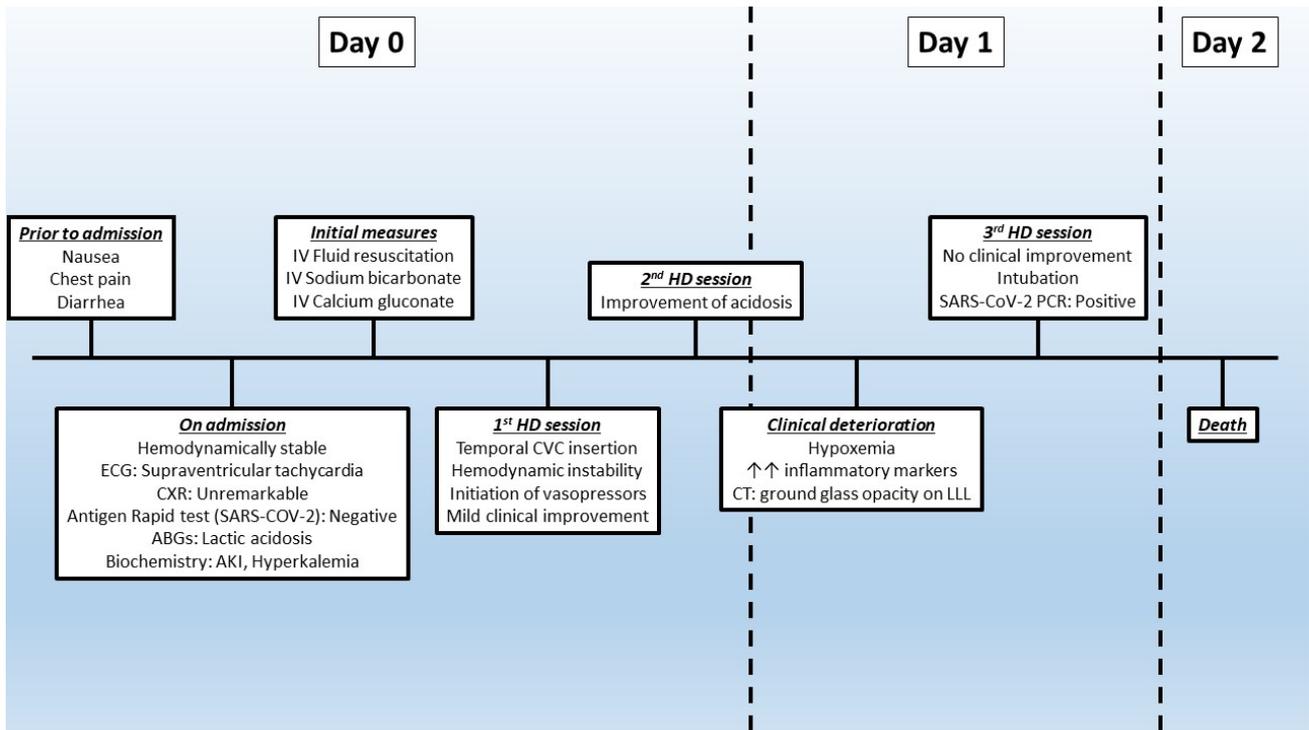
Fig. 1.   Timeline of the patient's clinical course. ECG, electrocardiogram; CXR, chest X-ray; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ABG, arterial blood gas; AKI, acute kidney injury; IV, intravenous; HD, hemodialysis; CVC, central venous catheter insertion; CT, computed tomography; LLL, left lower lobe; PCR, polymerase chain reaction.

ment [12, 13]. Hyperglycemia during or after vaccination against SARS-CoV-2 has also been related to an inadequate immune response, pointing towards a strict glycemic control in this specific time period [14].

Our patient presented with severe AKI secondary to COVID-19, with no previous evidence of kidney disease despite the presence of diabetes mellitus. However, DM is an independent predictor of AKI, a serious complication leading to increased morbidity and mortality [15]. Mechanisms of AKI in COVID-19 included but are not limited to direct viral kidney injury (endothelial dysfunction, inflammation, coagulopathy) or an indirect effect via fluid imbalance or drug nephrotoxicity [16]. The role of the cytokine storm and incident endothelial dysfunction in COVID-19 pathophysiology and complications is critical has been well-established [17–20], while the presence of comorbidities associated with pre-existing impaired endothelial function (age, arterial hypertension, cardiovascular disease) might be an aggravating factor contributing to renal complications [21, 22].

Metformin is the cornerstone of treatment and one of the most prescribed drugs in diabetic patients [23, 24]. Some studies have examined the potential benefits of metformin in COVID-19 patients, with encouraging results (Table 2, Ref. [25–34]). According to the study of Bramante *et al.* [25] which included 6256 patients, metformin use was associated with lower mortality in patients and especially obese or diabetic women hospitalized with COVID-19 by lowering tumor necrosis factor-α that has been detected in patients with T2DM as well as in lung tissue offended by SARS-CoV-2. Furthermore, some other retrospective studies concluded that death rates in metformin users are lower than non-users among COVID-19 patients [8]. It's noteworthy to refer that reduction in interleukin-6 was detected by some authors in metformin users [26].

Despite its beneficial action, lactic acidosis is considered a quite rare, potentially life-threatening complication with a mortality rate exceeding 50% in several studies [35, 36]. It is believed that 0 to 138 per 100,000 patients will develop MALA and this percentage may be increasing following the augmented prevalence of DM [35, 36].

MALA is characterized by: (a) pH lower than 7.35, (b) lactic acid >5 mmol/L, and (c) chronic or acute metformin use [37, 38]. The symptoms of MALA include hypotension, altered mental status preceded by gastrointestinal complaints such as diarrhea, nausea, and vomiting [37]. The values of lactate and pH are not prognostic factors whereas the coexistence of sepsis or renal failure is believed to be related to unfavorable outcomes [39]. Measurement of metformin levels is not required for the diagnosis and management, therefore they are not routinely ordered as in our case.

Based on a systematic review of MALA cases, the majority of the patients were exposed to other independent factors for lactic acidosis [38]. Usually, patients with

Table 2. The impact of metformin on COVID-19-associated outcomes.

Authors	Country	Number of patients	Result
Bramante *et al.* [25]	USA	6256	Decreased in-hospital death, especially in women
Luo *et al.* [27]	China	283	Decreased in-hospital death
Chen *et al.* [26]	China	120	No significant effect on duration of hospitalization, prognosis, in-hospital death
Cariou *et al.* [28]	France	1317	Lower death rate in day 7 in metformin users vs. no-users
Ghany *et al.* [29]	USA	1139	Lower mortality, rate of hospitalization and ARDS among metformin users especially obese
Li *et al.* [30]	China	131	Lower mortality rates for metformin users and in acarbose alone or in combination with metformin
Cheng *et al.* [31]	China	407	Lower intensive care unit admission in pre admission metformin usage
Wargny *et al.* [32]	France	2796	Metformin is a prognostic factor for hospital discharge and freedom from death
Crouse *et al.* [33]	USA	604	Reduced risk of mortality
Cheng *et al.* [34]	China	15451	Increased incidence of acidosis, reduced heart failure

USA, United States of America; ARDS, acute respiratory distress syndrome.

MALA exhibit many life-threatening comorbidities such as sepsis and kidney injury that lead to devastating outcomes [39]. In our patient, COVID-19 precipitated the acute renal impairment, further facilitating the incidence of MALA. In a retrospective study including 1213 individuals with COVID-19 and T2DM, metformin was associated with a high incidence of acidosis but not mortality [34]. The results of this study encourage continuing the usage of metformin but in severe cases of COVID-19 patients have to be monitored closely to avoid lactic acidosis and kidney dysfunction [34, 40]. In severe forms of COVID-19 serious gastrointestinal symptoms, hypoxia, or multiple organ dysfunction, metformin use is not indicated owing to the risk of lactic acidosis [8, 41]. However, as demonstrated in our patient initially the pulmonary infiltrates were limited, without suspicious symptomatology.

MALA treatment generally revolves around RRT to correct the underlying metabolic acidosis while also removing excess metformin [42]. Despite the very low quality of the available evidence, comprising mostly of case reports, the EXTRIP workgroup recommends RRT initiation in severe metformin poisoning cases (lactate >20 mmol/L, pH $\leq$7, and failure of standard therapy consisting of bicarbonate and hydration) [2]. In a recent analysis of a retrospective cohort study of 42 patients, RRT was not significantly associated with reduced mortality but results should be interpreted with caution due to the significant disparities in patient profiles of the examined groups [35]. Controversies also exist regarding the method, duration, and frequency of RRT as most approaches are based on expert opinions and case reports [43, 44]. Recent reports have studied prolonged dialysis regimens, namely sustained low-efficiency dialysis (SLED), noting lower mortality rates [45]. This RRT method combines hemodynamic stability and more effective drug clearance than continuous RRT paired with a decrease in rebound phenomena [3] owing to metformin accumulation in peripheral tissues and erythrocytes according to pharmacokinetic studies [46]. However, institutional limitations are frequently present with regards to SLED implementation and, alternatively, multiple daily intermittent hemodialysis sessions can be arranged. Our treatment approach, consisting of twice-daily 4-hour hemodialysis sessions, resulted in improvement of MALA but the patient's condition deteriorated and ultimately led to death due to the respiratory complications of COVID-19.

5. Conclusions

Lactic acidosis is a relatively rare but noteworthy complication of metformin use since it is associated with high rates of mortality. The prompt recognition of this medical condition is of paramount importance, in the era of COVID-19, since delays in its diagnosis and management could end up being fatal. RRT is the mainstay of treatment to correct the underlying metabolic acidosis while also removing excess metformin.

Metformin use is associated with favorable outcomes in COVID-19 according to published studies. However, appropriate medical care should be provided to patients who develop AKI, a frequent COVID-19 complication associated with a worse prognosis. Therefore emphasis should be given towards metformin discontinuation in cases of abdominal pain and repeated diarrhea which are frequent atypical symptoms of SARS-CoV-2 infection, intending to avoid incident catastrophic side effects such as MALA. Future research should further investigate the importance of AKI with co-existing acidosis with regards to prognosis in COVID-19.

6. Author contributions

AV and PT contributed to the design of the work, drafted the manuscript, and gave final approval of the version published. GV, MK and RGK contributed to the design of the work, critically revised the manuscript, and gave final approval of the version published.

7. Ethics approval and consent to participate

Written informed consent was obtained from the patient's next-of-kin for publication of this case report.

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10. Conflict of interest

The authors declare no conflict of interest.

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