Severe metformin-associated lactic acidosis in the setting of diabetic nephropathy

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Introduction

- Metformin is a commonly prescribed medication used as initial therapy for patients with pre-diabetes and diabetes.
- In general, it is a safe medication with its main side effect being gastrointestinal upset. However, a rare (<10 cases per 100,000 patient-years) but life-threatening adverse effect is lactic acidosis.
- Lactic acidosis is an important side effect that is well documented but it's rare. Despite its rare incidence it has a mortality rate that approaches 50%.

Case Presentation

70-year-old woman with a history of coronary artery disease with history of myocardial infarction status post coronary artery bypass grafting (CABG), systolic heart failure (ejection fraction 40-45%) status post automatic implantable cardioverter-defibrillator (AICD) placement, type 2 diabetes mellitus, and hypertension. She reported two weeks of progressively worsening shortness of breath. Reported associated symptoms of palpitations, nausea, dyspnea on exertion, and orthopnea.

Physical exam was notable for dyspnea, tachypnea, and decreased breath sounds. Initial blood counts showed mild leukocytosis to 9.9 and mild anemia with hemoglobin of 11.1. Initial glucose was 128, elevated potassium of 5.5, undetectable serum bicarbonate, and anion gap of 32. Negative serum alcohol level. Kidney function was decreased with BUN of 37 and creatinine of 2.7. BNP was elevated to 40,000. Hemoglobin A1c was elevated to 10.5. Lactic acid was 19.4.

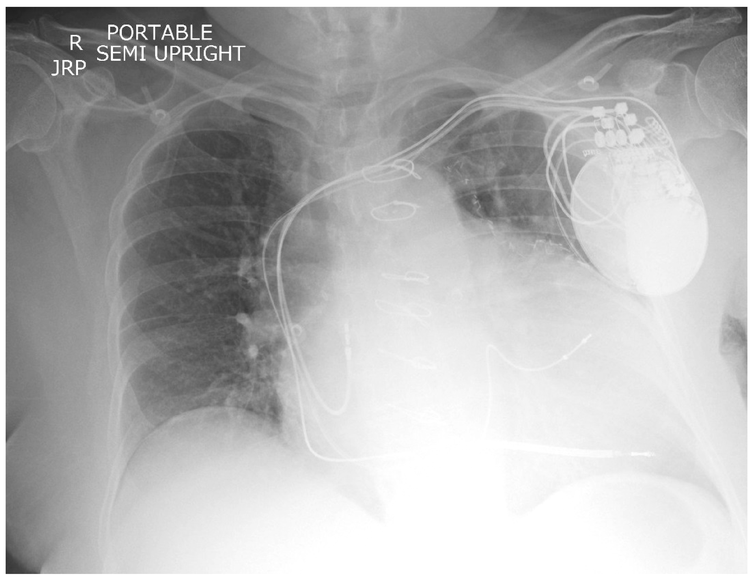

Figure 1 – Initial chest x-ray

Chest x-ray showed cardiomegaly with no acute cardiopulmonary findings, sternal wires, and AICD (Figure 1). Patient was started on supplemental oxygen and bicarbonate drip. ABG showed pH 7.25, paCO2 13.8, paO2 173, HCO3 5.9 on 5 L NC.

Creatinine kinase was mildly elevated to 816. Serum osmolality was high at 334 and no osmolar gap. Intact parathyroid hormone significantly increased to 161, most likely due to underlying CKD at least stage 4. Nephrotic-range proteinuria with protein/creatinine ratio of 6.6 grams. Direct urine microscopy was performed with no evidence of calcium oxalate crystals. Patient developed increased work of breathing and was started on BiPAP. Despite intervention the lactic acid levels continued to increase to 23.5.

Early morning on hospital day 2, overnight team was called to bedside. The patient had developed bleeding from oral mucosa, peripheral IV sites, and to have hematuria. Laboratory evaluation showed WBC to 16.3, Hgb 9.2, d-dimer >25,000 ng/ml, PTT 52 (normal 25-36), PT 171 (normal 9.5-12.7), INR 14.7, AST 2720, ALT 574, and lipase 1002. Disseminated intravascular coagulation (DIC) was suspected and patient was emergently transferred to the medical intensive care unit. Abnormal coagulation testing also likely due to home rivaroxaban patient had been taking.

Blood products were given including packed red blood cells, fresh frozen platelets, tranexamic acid, and vitamin K. Lactic acid levels remained elevated and nephrology team started patient on hemodialysis. She initially received conventional hemodialysis followed by continuous renal replacement therapy (CRRT).

Patient continued to deteriorate and was intubated for airway protection. Approximately an hour later, the patient developed pulseless electrical activity (PEA) and Code Blue was called. Return of spontaneous circulation (ROSC) was obtained then patient subsequently coded two more times. Patient's family decided to make patient do not resuscitate and she ultimately expired.

Discussion

Lactic acidosis may be a rare complication of a common and generally safe drug, but it is an important condition to clinically recognize. The severity of illness and need for urgent intervention makes timely diagnosis crucial. It can be especially difficult to diagnose in patients with multiple comorbidities. Chronically ill patients are at higher risk for morbidity and mortality.

Chronic kidney disease, seen in this patient, and liver disease are notable risks for poor prognosis. The serum metformin doesn't correlate with disease severity and is not routinely used in suspected metformin toxicity. Metformin toxicity may be associated with acute ingestion. It can also be present in the setting of chronic use, usually related to poor renal clearance in CKD. Hemodialysis was indicated in this patient because the lactic acid levels remained above 20. This patient expired despite intervention consistent with the high mortality rate seen in this condition.

	Day 1	Day 2
WBC	9.9	16.3
Hgb	11.1	9.2
Platelet	244	165
BNP	40,000	
K	5.5	5.1
Bicarbonate	<5	14
Creatine kinase	816	1,589
Lactic acid	19.4	23.5
INR		14.7
D-dimer		25,442
Lipase		1,002

Table 1 – Inpatient laboratory studies

Conclusion

- Metformin is a common medication used extensively to manage pre-diabetes and diabetes with generally benign adverse effects apart from lactic acidosis.
- Metformin toxicity should be considered early during evaluation of an otherwise unexplained severe lactic acidosis as mortality is high and patients frequently require prompt initiation of hemodialysis.

References

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