Case Report

A case of type 2 diabetes mellitus with metformin-associated lactic acidosis initially presenting the appearance of a sulfonylurea-related hypoglycemic attack

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Case: A 64-year-old Japanese woman with diabetes mellitus was admitted for hypoglycemia. Her diabetes had been under good control with glimepiride, voglibose, exenatide, and metformin for a few years. Although overt proteinuria was observed, the serum creatinine values were within normal range during the routine outpatient follow-up. Hypoglycemic attack caused by glimepiride and loss of appetite by urinary tract infection were diagnosed. Then, metformin-associated lactic acidosis with acute renal failure caused by dehydration was detected.

Outcome: Her condition was improved by continuous veno-venous hemodiafiltration and hemodialysis, known to be useful to remove metformin.

Conclusion: We reported a case of metformin-associated lactic acidosis with hypoglycemia during routine treatment of diabetes that was successfully rescued by early renal replacement therapy.

Key words: Diabetes mellitus, hemodialysis, hypoglycemia, lactic acidosis, metformin

INTRODUCTION

METFORMIN IS AN antidiabetic agent of the biguanide family used as a first choice medication for type 2 diabetes mellitus. Metformin-associated lactic acidosis (MALA) is a severe adverse effect of metformin with a mortality rate of 50%.1 Metformin-associated lactic acidosis may occur with hypoglycemia of 12.2%.2 Here, we report a case of type 2 diabetic mellitus with MALA treated with four hypoglycemic agents, including metformin. Severe hypoglycemia with rapidly progressive lactic acidosis was observed and the patient recovered with continuous venovenous hemodiafiltration (CVVHDF) and hemodialysis.

CASE

THE PATIENT WAS a 64-year-old Japanese woman with a 20-year history of type 2 diabetes mellitus complicated with hypertension, dyslipidemia, and incomplete right paresis caused by cerebral infarction. She had diabetic nephropathy with overt proteinuria and proliferative retinopathy. She has been treated with the following medications: metformin 2,250 mg/day, glimepiride 1 mg/day, voglibose 0.9 mg/day, exenatide 20 μg/day, candesartan 8 mg/day, olmesartan 20 mg/day, amlodipine 5 mg/day, rosuvastatin 2.5 mg/day, tocothoprol 600 mg/day, and polaprezinc 150 mg/day. Seven days before admission, her glycated hemoglobin was 5.6% (NGSP), serum creatinine was 0.76 mg/dL, and urinary protein was 1.85 g/g creatinine. She was admitted to Mie University Hospital (Tsu, Japan) because of general fatigue and bilateral leg edema. She complained of mild fever, fatigue, anorexia, and leg edema from 1 week before admission, and the symptoms were getting progressively worse. She was taking metformin...
and glimepiride until the evening of the day before her hospital visit. The clinical findings on examination were as follows: height, 155 cm; body weight, 77.2 kg; Glasgow Coma Scale, 15; blood pressure, 116/51 mmHg; heart rate, 90 b.p.m.; respiratory rate, 18 breaths/min; body temperature, 36.3°C; and peripheral oxygen saturation (SpO2), 84% (room air). Physical examination showed right costovertebral angle tenderness and bilateral leg pitting edema with tenderness. Laboratory data disclosed a blood glucose level of 42 mg/dL measured with a portable device and then confirmed by an analysis performed at the laboratory of Mie University Hospital; there was also severe renal dysfunction, high levels of C-reactive protein, and leukocytosis (Table 1). Arterial blood gas analysis showed metabolic acidosis and increased blood lactic acid level. Urinalysis and urinary sediment suggested urinary tract infection (urine culture positive for *Escherichia coli*). Computed tomography revealed bilateral leg edema. The diagnoses on admission were hypoglycemia, lactic acidosis, urinary tract infection, and dehydration with peripheral circulatory failure-associated acute renal injury.

After admission, the patient was treated with i.v. fluid, bicarbonate, and ceftriaxone. However, despite i.v. fluid (2,000 mL/8 h) and bicarbonate therapy, no improvement in lactic acidosis or oliguria was observed. Therefore, the patient was first treated with CVVHDF. Her condition improved after 16 h of CVVHDF, and hemodialysis were subsequently undertaken for 3 h. These treatments improved lactic acidosis, renal function, and the acid-based disturbance (Fig. 1). The plasma metformin concentration on admission was 31.1 µg/mL, which is approximately 10-fold higher than the concentration observed in patients taking regular doses (850 mg) of metformin. After recovery from MALA and urinary tract infection, the patient was discharged on day 30 with the therapeutic indication of insulin glargine (10 units/day) and vildagliptin (50 mg/day).

**DISCUSSION**

**METFORMIN-ASSOCIATED** lactic acidosis is a rare but a life-threatening adverse effect of metformin; the reported mortality rate of MALA is approximately 50%. A

| Table 1. Laboratory data on admission of a 64-year-old woman with type 2 diabetes mellitus and metformin-associated lactic acidosis |
|-------------|----------------|------------|
| **Blood cell count** | **Biochemical examination** | **Arterial blood gas analysis (room air)** |
| White blood cells | 16,790/µL | HbA1c | 6.2% |
| Red blood cells | 326 × 10⁹/µL | Glucose | 29 mg/dL |
| Hemoglobin | 9.1 g/dL | Total protein | 5.7 g/dL |
| Hematocrit | 28.6% | Albumin | 3.0 g/dL |
| MCV | 87.7 fl | BUN | 54 mg/dL |
| MCH | 27.9 pg | Creatinine | 4.4 mg/dL |
| Platelets | 40.4 × 10⁹/µL | Uric acid | 9.2 mg/dL |
| **Urinalysis** | | Na | 135 mEq/L |
| Specific gravity | 1.011 | K | 5.7 mEq/L |
| pH | 5.0 | Cl | 100 mEq/L |
| Glucose | (−) | Ca | 8.1 mg/dL |
| Protein | (+) | P | 7.7 mg/dL |
| Ketone body | (−) | AST | 13 U/L |
| Blood | (2+) | ALT | 7 U/L |
| **Blood** | | LDH | 201 U/L |
| **γ-GTP** | | ALP | 18 U/L |
| **ALP** | | CRP | 327 U/L |
| **Red blood cells** | | T-Bil | 0.2 mg/dL |
| **White blood cells** | | CRP | 33.76 mg/dL |

†Normal range of blood lactate level, 0.9–1.7 mmol/L. ‡Measured 7 days before admission (random blood glucose). §Urine culture isolated *Escherichia coli*. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium; Cl, chloride; CRP, C-reactive protein; γ-GTP, γ-glutamyl transferase; HbA1c, glycated hemoglobin; HPO4, high power field; K, potassium; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; Na, sodium; P, phosphorus; T-Bil, total bilirubin.
recent report suggested that the risk of MALA was significantly associated with impaired renal function and high dosage of metformin.\textsuperscript{4} Prescribing information for metformin also warns that renal insufficiency, dehydration, and hypoxemia may cause MALA.\textsuperscript{3} The mechanism of MALA is still not clear. It is assumed that metformin induces lactic acid accumulation by an intracellular shift in oxidation-reduction reactions from aerobic to anaerobic metabolism. Accumulation of lactic acid reduces intracellular pH that inhibits pyruvate carboxylase and dehydrogenase, leading to increased lactic acid accumulation.\textsuperscript{5} Disturbed insulin secretion and action may worsen this pathological state.

This case presented many risk factors for MALA. The high blood levels of metformin observed in the current case could be explained by the high dose of metformin and possible overestimation of the patient’s renal function based on the serum creatinine level, because of muscular atrophy following cerebral infarction and hemiparesis. Although the body weight of the patient was high, she had multiple comorbidities including diabetes, hypertension, dyslipidemia, and stroke that were probably associated with sarcopenic obesity.\textsuperscript{6} The angiotensin II receptor antagonist that the patient was receiving may explain the deterioration in renal dysfunction during dehydration. Hypoxia is an aggravating factor of MALA that may be caused by impaired ventilation due to obesity-associated glossoptosis. In addition, decreased oral intake and continuous use of oral hypoglycemic agents may cause hypoglycemia. Hypoglycemia raises the level of blood lactic acid by increasing blood epinephrine levels\textsuperscript{7} and glycogenolysis in skeletal muscles.\textsuperscript{8} Therefore, it is conceivable that MALA had a progressive clinical course due to complicated hypoglycemia.

In general, MALA is treated by hemodialysis and bicarbonate. Hemodialysis is very useful to remove metformin because of low molecular weight, lack of protein binding, high water solubility, and broad tissue distribution of metformin. Previous reports suggested that hemodialysis improves acid–base imbalance and it is considered the most effective treatment for patients with severe MALA.\textsuperscript{5,9,10} Suggested criteria for implementation of renal replacement therapy in patients with MALA are severe acidosis (pH < 7.1), poor response to standard treatment, and renal insufficiency.\textsuperscript{9}

Based on the patient’s poor response to initial therapy, we started renal replacement therapy. As her blood pressure was 20% lower than usual, we used CVVHDF to perform dialysis with low blood pressure. The therapy was then changed to hemodialysis in order to increase the removal efficiency of metformin, and after the blood pressure of the patient improved with CVVHDF for 16 h (Fig. 1). After this, the urine volume gradually increased and lactic acidosis was ameliorated by hemodialysis. A
previous report has questioned the usefulness of continuous veno-venous hemofiltration for MALA,\textsuperscript{11} however, we think that the quick change from CVVHDF to hemodialysis, which has higher removal efficiency, led to the rescue of this patient.

In conclusion, this is a well-detailed report of MALA with hypoglycemia during routine treatment of diabetes, rescued by the combined therapy of CVVHDF and hemodialysis. We should take into consideration the diagnosis of MALA when we have a patient treated with metformin, even if the patient shows the appearance of common hypoglycemic attack. Once the diagnosis of MALA is confirmed, renal replacement therapy should be considered as soon as possible. Early diagnosis of MALA and renal replacement therapy is important to rescue MALA patients with sulfonylurea-related hypoglycemic attack.

CONFLICT OF INTEREST

NONE.

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