CASE REPORT

Diabetic Ketoacidosis Associated With Acute Pancreatitis in a Heart Transplant Recipient Treated With Tacrolimus

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Abstract

New-onset diabetes mellitus after transplant is a well-recognized complication of tacrolimus immunosuppression and commonly occurs as a form of type 2 diabetes mellitus. However, tacrolimus-associated acute pancreatitis causing diabetic ketoacidosis has not been reported in heart transplant patients.

We report a 22-year-old women hospitalized owing to diabetic ketoacidosis associated with acute pancreatitis 7 months after a heart transplant. Her immunosuppression included tacrolimus. She was admitted with complaints of polydipsia, anorexia, and abdominal pain of 3 days' duration. Her initial laboratory test revealed a toxic level of tacrolimus (> 30 ng/mL), severe hyperglycemia (39 mmol/L), severe metabolic acidosis (pH 6.9), and ketonuria, although diabetes mellitus had never been diagnosed. Serum amylase and lipase levels and abdominal computed tomography suggested the presence of acute pancreatitis. After correcting the diabetic ketoacidosis and getting the tacrolimus level to the normal range, she was discharged home. Three months later, insulin was replaced with oral hypoglycemic agents.

Pancreatitis can present with diabetic ketoacidosis in the recipient of a heart transplant treated with tacrolimus. Clinicians should pay more attention to tacrolimus levels and the risk of pancreatitis.

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Introduction

New-onset diabetes mellitus after transplant, an important complication after all kinds of solid-organ transplants, occurs in 2% to 53% of patients receiving tacrolimus.[1] Regarding heart transplants, the wide adoption of tacrolimus replacing cyclosporine as a main immunosuppressive agent increases the risk of diabetes mellitus to more than 25% of new-onset diabetes mellitus after transplant during a mean follow-up of 2 years.[2] Diabetic ketoacidosis (DKA) has been reported as initially presenting in kidney and liver transplant recipients.[3,4] Three cases of acute pancreatitis possibly associated with tacrolimus also were reported in allogeneic stem cell transplant and kidney transplants.[5,6] However, as far as we know, there have been no cases after a heart transplant. Reported here is one case of DKA associated with acute pancreatitis in a female heart transplant recipient prescribed tacrolimus for immunosuppression.

Case Report

A 22-year-old woman, who had received a heart transplant 7 months earlier was admitted to the emergency department with complaints of polydipsia, anorexia, and abdominal pain of 3 days' duration.

Seven months earlier, she had undergone a cardiac transplant for intractable ventricular tachycardia with dilated cardiomyopathy, with a heart donated by a male donor. Her initial immunosuppressive regimen consisted of tacrolimus, corticosteroids, and mycophenolate mofetil. However, she was unable to tolerate even

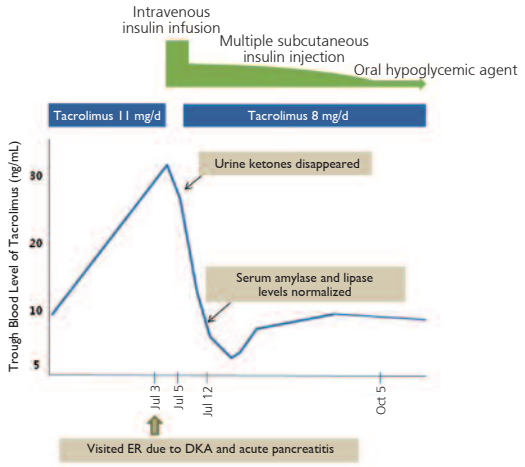
low dosages of it (250 mg twice daily), having been admitted to the hospital, twice, for neutropenic fever. After recovering an absolute neutrophil count to 1500, her immunosuppression protocol was changed over to tacrolimus and corticosteroids, without any evidence of recurrent rejection. During 6 months of follow-up, the corticosteroids were successfully tapered, and only tacrolimus was maintained at a dosage of 11 mg/d (0.19 mg/kg/d), and the trough blood level was within target range of 11.3 to 11.6 ng/mL.

Before this, there was no evidence of hyperglycemia on routine blood chemistry test. She was not obese (158 cm, 49 kg, BMI = 22.43 kg/m^2) and had no family history of diabetes mellitus. At the time of emergency department admission, her blood pressure was 130/80 mm Hg, her pulse rate was 126 beats/minute, her respiratory rate was 35 inspirations/minute, and her body temperature was 36.8°C. On physical examination, she showed a dehydrated tongue and diffuse abdominal tenderness. Her initial laboratory tests revealed a leukocyte count of 12 500/mm^3, a serum glucose of 39 mmol/L, and a serum creatinine level of 114 μmol/L. Her hemoglobin A1C level was 12.1% and plasma C-peptide was 0.23 mmol/L. Initial arterial blood gas analysis showed pH 6.9, PCO_2 7.1 mm Hg, PO2 154 mm Hg, HCO3- 4.0 mmol/L, and the initial anion gap was calculated as 33.8 mmol/L. Urinalysis showed glycosuria and strong positivity for ketonuria. Blood chemistry was also suggestive of the presence of acute pancreatitis: serum amylase 29 μkat/L and lipase 32 μkat/L. An abdominal computed tomography scan showed pancreatic swelling, especially in the head portion, with peripancreatic fluid collection consistent with acute pancreatitis. There were no signs of systemic infection on physical examination. Remarkably, trough blood levels of tacrolimus were reported as higher than the assay limits (> 30 ng/mL).

Based on these findings, a diagnosis of DKA was made, and she was treated with intravenous saline, sodium bicarbonate, and continuous insulin infusion. Tacrolimus was skipped for 2 days and restarted with 4 mg twice daily once the trough level was adjusted to 8.4 ng/mL. Forty-six hours after her admission, her arterial pH and serum anion gap were normalized, and the urine ketone disappeared. Her creatinine level also decreased to 114.9 μmol/L. After 9 days, serum amylase and lipase levels also were normalized.

From hospital day 2, she was gradually switched from intravenous insulin to the subcutaneous form. Her initial insulin requirement was 45 IU per day; however, that requirement was rapidly decreased. Three months later, she began oral hypoglycemic agents (gliclazide, sitagliptin, and metformin) (Figure 1).

Figure 1. Time Course of Trough Blood Level of Tacrolimus



Abbreviations: DKA, diabetic ketoacidosis; ER, emergency department
Dosage of tacrolimus was skipped for 2 days and restarted with 4 mg twice daily.

Discussion

Diabetes mellitus after an organ transplant has been associated with the use of immunosuppressive drugs. However, to the best of our knowledge, acute pancreatitis causing DKA has not been previously reported in a heart transplant recipient receiving tacrolimus.

Tacrolimus may produce β-cell toxicity, reduce insulin synthesis or release, and decrease peripheral insulin sensitivity.[7] Several in vitro studies have shown β-cell impairment with high-dose tacrolimus.[8] For 2 months preceding the aforementioned event of our patient, trough levels of tacrolimus were well controlled from 6.4 to 11.6 ng/mL. However, the tacrolimus level at the time of admission was higher than the assay limits (> 30 ng/mL). Therefore, we presumed that DKA associated with acute pancreatitis may have been caused by β-cell dysfunction associated with the sudden increase in

her tacrolimus concentrations. Additionally, rapidly decreased insulin requirement after this event is also suggestive of transient pancreatic damage by toxic levels of tacrolimus. Other possible causes could be the following: the cumulative dosage of steroids were too small to induce acute pancreatitis and steroids were tapered and discontinued 1 month prior to her pancreatitis episode.

Cytomegalovirus IgM antibody was nonreactive, and *Cytomegalovirus* IgG antibody was reactive (225.0 AU/mL) before heart transplant. *Cytomegalovirus* antigen had never been positive before and after DKA. Other common causes of acute pancreatitis such as biliary obstruction, alcohol, or hypercalcemia were excluded by abdominal computed tomography and laboratory tests. The cause of the patient's abrupt increase in her tacrolimus level was not clarified even though a meticulous history was obtained.

We reported a case of severe pancreatitis causing DKA in a female heart transplant recipient prescribed tacrolimus for immunosuppression. The case suggests that acute pancreatitis may present with DKA in the recipient of a heart transplant treated with tacrolimus. Clinicians should pay more attention to tacrolimus levels and the risk of pancreatitis.

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