Rapid Recovery of Diabetes Two Months after Discontinuation of Tacrolimus (FK-506) in a Single Lung Transplant Patient

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ABSTRACT
Post-transplant diabetes mellitus (PTDM), developing in almost one quarter of renal transplant patients within three years after the procedure, contributes to post-transplant morbidity and mortality by increasing the risk of infection and cardiovascular events. PTDM is considered a variant of diabetes mellitus (DM) type II and results in similar microvascular and macrovascular diabetic complications seen in non-transplant patients. In this article, we present a case of single lung transplant patient who developed PTDM with a severe DKA as the first manifestation of the disease. PTDM resolved rapidly after discontinuing tacrolimus. (Tanaffos 2009; 8(4): 55-59)

Key words: Diabetic ketoacidosis, Immunosuppressive agents, Adverse effects, Tacrolimus, Treatment outcome, Lung transplantation

INTRODUCTION
Post-transplant diabetes mellitus (PTDM), developing in almost one quarter of renal transplant patients within three years after the procedure (1), contributes to post-transplant morbidity and mortality by increasing the risk of infection and cardiovascular events (2-4). PTDM is considered a variant of diabetes mellitus (DM) type II (5) and results in similar microvascular and macrovascular diabetic complications seen in non-transplant patients (3). However, PTDM-related complications progress more rapidly in renal transplanted patients (3), adversely affecting the allograft and patients’ survival. In addition to the same known risk factors predisposing the general population to DM, the choice of immunosuppressive regimen used for transplant maintenance therapy has also been demonstrated to be an independent risk factor for developing PTDM. For instance, Kasiske et al., in a study on 11,659 renal transplant cases, revealed that the risk of PTDM was significantly higher among patients who received tacrolimus compared to those on non-tacrolimus based maintenance therapy (1). Cyclosporine (CsA), another calcineurin inhibitor, has also been found to be associated with a significantly higher incidence of glucose intolerance.
Based on these observations, pre and post transplant screening for PTDM is recommended to determine the risk of diabetes in transplant patients and diagnose the disease earlier, prior to the development of common clinical manifestations of PTDM. Development of diabetic ketoacidosis (DKA) as the first manifestation of PTDM has been rarely reported among transplant recipients with no prior diagnosis of DM (7, 8). In this study, we present a case of single lung transplant patient who developed PTDM with a severe DKA as the first manifestation of the disease. PTDM resolved rapidly after discontinuing tacrolimus.

**CASE SUMMARIES**

Our patient was a 41-year-old man, with a history of dry cough and progressive exertional dyspnea from childhood and end-stage lung disease due to idiopathic pulmonary fibrosis who received a left lung transplant from a blood type B positive 26 year-old male donor in August 2005.

His post-operative course was uneventful. He was discharged on CsA, mycophenolate mofetil (MMF) and tapering doses of prednisone and remained clinically stable with no decline in pulmonary function for the subsequent two months.

In Nov. 2005, the patient developed a markedly progressive dyspnea and his pulmonary function tests (PFT) deteriorated. Transbronchial lung biopsy (TBLB) revealed acute rejection grade 2-3. Further evaluation also demonstrated simultaneous fungal and bacterial infection (endobronchial aspergillosis and positive culture for acinetobacter). Therefore, steroid pulse therapy was not prescribed. Antifungal and antibacterial agents were initiated and tacrolimus (5mg/BID) was substituted for high dose CsA (serum level of 380) which was being used as the maintenance therapy when the rejection occurred. Patient’s symptoms resolved one week later.

Forty five days post-tacrolimus, the patient suffered from polyuria and polydipsia and his fasting blood sugar raised to 180 mg/dl. Tacrolimus dosage was lowered.

Three days later, he was admitted because of malaise, abdominal pain and severe vomiting. Physical examination revealed an ill-appearing, severely dehydrated man with dry mucous membranes and reduced skin turgor. His blood pressure was 100/60 mmHg, heart rate 128/min, respiratory rate 20/min and temperature 37.3 °C. His level of consciousness was normal without focal neurological deficit. No abnormalities were noted on physical examination except for a generalized abdominal tenderness and the ketone smell on breath. There was no evidence of infection on physical examination. Laboratory findings showed a serum glucose level of 1400 mg/dl, serum sodium of 130 mEq/L and potassium of 6.1 mEq/L. There was a metabolic acidosis with pH: 7.28, PCO2: 36.6 mmHg, HCO3: 16.9 mmol/L, base deficit: 9.8 mmol/L and PO2: 92.2% without oxygen administration. Urinalysis revealed 2+ ketone; whereas, he had not taken any drugs to cause false positive ketonuria. Blood culture was negative (After 48 hours and 10 days). A diagnosis of DKA was made. His blood sugar was within the normal range before and two months after transplantation (Table 1). He weighed 65 Kg, his family history revealed that his father had diabetes mellitus (Type II) and his HCV Ab was not reactive.

The patient was treated with fluid replacement therapy and insulin infusion. CsA was substituted for tacrolimus. His clinical condition improved rapidly and he was gradually switched to subcutaneous insulin. He was discharged on a total daily dose of 38 units of insulin.

Insulin dose was lowered subsequently and discontinued two months later. The patient’s blood glucose level remained within the normal range with no rise afterward.
DISCUSSION

The choice of immunosuppressive regimen is critical for achieving optimal long-term graft survival. Treatment of lung transplant recipients often poses unique challenges to the internist. The current strategy is to select an immunosuppressive regimen based not only on its effectiveness in preventing acute rejection, but also on its ability to minimize side effects.

Development of PTDM and its related complications are among the side effects that should be expected in a transplant patient whether with or without a prior diagnosis of DM.

There are many postulated mechanisms for the development of PTDM. Corticosteroids and CsA are all known to affect carbohydrate metabolism by increasing insulin resistance and also decreasing insulin secretion. The effects of corticosteroids on glucose metabolism have been extensively reviewed, and decreased glucose utilization and increased hepatic glucose production have been well recognized as the primary defects (9). CsA inhibits insulin secretion from the beta cells (10) and decreases glucose disposal (11).

Tacrolimus, a macrolide immunosuppressant that acts by inhibiting cell-mediated and, to a lesser extent, humoral immunity, has been demonstrated to be more diabetogenic than CsA (12-14).

Although the exact diabetogenic mechanism(s) of tacrolimus has not been elucidated, it is speculated that it may lead to PTDM by 1) increasing peripheral insulin resistance and 2) impairing insulin secretion from pancreatic β-cells (15, 16).

Although the causality was not conclusively proven in this patient, the development of PTDM following the substitution of tacrolimus for CsA and its rapid resolution after tacrolimus discontinuation, suggests tacrolimus as the main contributing factor for development of PTDM in this patient. We speculate that a substantial degree of β-cell impairment or enhanced peripheral insulin resistance, or a combination of these two effects, might be the pathogenesis behind DKA in this patient.

Also, despite severe hyperglycemia and marked ketosis noted at initial presentation of PTDM, the patient’s demand for insulin reduced and his PTDM completely resolved within two months, soon after substitution of CsA for tacrolimus. The reversible toxicity of tacrolimus to β-cells has been documented by previous studies. In an animal model, tacrolimus induced vacuolization within β-cells that returned to normal within two weeks of discontinuation of the drug (17, 18). It has also been demonstrated that tacrolimus reversibly suppresses insulin gene transcription (19). PTDM has been shown to be reversible in human subjects, as well (20-22). About one-quarter to one-third of affected tacrolimus recipients were able to discontinue insulin therapy within 1 year in major renal clinical trials (23, 24).
However, to the best of our knowledge, the predicting factors for the reversibility of tacrolimus-induced PTDM have not yet been established. Our case indicated that PTDM might be reversible regardless of the severity of toxicity.

Despite its greater diabetogenic profile, tacrolimus has been shown to provide a more efficient rescue therapy in transplant recipients with persistent acute or chronic allograft rejection (15). Importantly, in lung transplant recipients with obliterative bronchiolitis, conversion to tacrolimus either reduced the decline or improved lung function in terms of forced expiratory volume in 1 second (15). Therefore, pre-transplantation risk assessment and modification of the immunosuppressive regimen are recommended based on the patient’s potential benefits and harms. Where possible, diabetogenic immunosuppressant regimen should be avoided in high risk patients. In addition, as seen in this patient, PTDM should be expected early so that immediate intervention may avoid severe consequences to the graft and the patient.

REFERENCES