Tacrolimus-Associated Diabetic Ketoacidosis: A Case Report and Literature Review

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Abstract

Post-transplant diabetes mellitus is a well-established adverse effect of calcineurin inhibitors, such as tacrolimus and cyclosporine. Failure to identify and manage this side effect in a timely manner could lead to life-threatening complications like diabetic ketoacidosis (DKA). To the best of our knowledge, this is the seventh published case of an uncommon but severe, and potentially fatal, adverse effect from tacrolimus after renal transplantation. The purpose of this case report is to add to the scant body of literature on tacrolimus-induced diabetes following renal transplantation.

Introduction

New-onset diabetes mellitus after transplantation (NODAT) is a well-established adverse effect of calcineurin inhibitors, such as tacrolimus and cyclosporine. NODAT has been reported to occur in 13.4% of patients after solid organ transplantation, with a higher incidence in patients receiving tacrolimus than cyclosporine, 16.6% and 9.8% respectively (1). Failure to identify and manage this side effect in a timely manner could lead to life-threatening complications like diabetic ketoacidosis (DKA). Currently, only seven reported cases, including this report, of NODAT with DKA exist in the English literature. This case report describes a patient who developed tacrolimus-induced diabetic ketoacidosis three months after receiving renal transplantation.

Case Description

The patient is a 44-year-old Caucasian male with no past medical history of diabetes mellitus who presented with diabetic ketoacidosis three months after receiving a deceased-donor kidney transplant for end stage renal disease secondary to autosomal dominant polycystic kidney disease. The patient's immunosuppressive regimen included tacrolimus, mycophenolate and low dose prednisone (5 mg daily). The patient initially

presented with complaints of nausea and polyuria. He did not have a family history of diabetes mellitus. Physical examination was unremarkable except for a body mass index (BMI) of 27 kg/m^2. Laboratory work-up revealed hyperglycemia with a glucose of 493; an anion gap metabolic acidosis with pH at 7.32 and bicarbonate at 19; significant ketosis; and ketonuria. Glycated hemoglobin (hemoglobin A1c) was 9.8 % compared to 4.8% thirty days post-transplant. Tacrolimus trough level was in the therapeutic range. Glutamic acid decarboxylase (GAD-65) autoantibodies were negative. The patient received intravenous fluids, a bolus of intravenous insulin followed by a continuous insulin infusion which was soon switched to subcutaneous insulin. Upon resolution of the patients DKA, the total daily maintenance insulin requirements were approximately 40 units. The patient received diabetic education and was discharged home.

Discussion

At the time of writing this report, there were only six reported cases of NODAT following the use of cyclosporine inhibitors such as tacrolimus which are summarized in table 1 (2-7).

Table 1. Summary of the seven reported cases focused on clinical presentation and management.

	Age, Sex	Transplanted Organ	BMI	Time passed from Transplantation	Maintenance Immunosuppressant regimen	Outcome
Our Patient	44 M	Kidney	27	3 mo	TAC + PDN + MPS	DM Controlled on SC Insulin
Cho, 2002	35 F	Kidney	21.8	6 mo	TAC + PDL + MMF	DM controlled on Diet Tx alone
Dehghani, 2008 (1)	13 F	Liver	NA	7 mo	TAC + MMF	Death 2/2 Sepsis
Dehghani, 2008 (2)	14 M	Liver	NA	3 mo	TAC + PDL	DM Controlled on SC Insulin
Dehghani, 2008 (3)	14 M	Liver	NA	4 mo	TAC + MMF	DM Controlled on SC Insulin
Ersoy, 2004	42 F	Kidney	29.8	3 yr	TAC + PDL + AZT	DM controlled on SC insulin (only for initial 6 mo) and acarbose
Im, 2013	22 F	Heart	22.43	7 mo	TAC	DM Controlled on SC Insulin, gliclazide, sitagliptin, metformin
Keshavarz, 2002	14 F	Liver	NA	1 yr	TAC + PDN	DM Controlled on SC Insulin
Masood, 2011 (1)	17 M	Kidney	NA ("Marked Obesity")	1 yr	TAC +PDL + MMF	DM Controlled on SC Insulin
Masood, 2011 (2)	55 F	Liver	NA	2 yr	TAC +PDL + MMF	DM Controlled on SC Insulin
Öztürk, 2015	17 M	Heart	15.4	3 mo	TAC +PDL + MMF	DM Controlled on SC Insulin
Solmaz, 2015	24 F	BM	20.8	70 days	TAC	NA ("Discharged Home")
Toyonaga, 2002	43 M	Kidney	18.2	1 yr	TAC + MPL	DM controlled on Diet Tx alone
Tuğcu, 2015	44 M	Kidney	NA	5 wk	TAC + PDL + MMF	DM Controlled on SC Insulin
Yoshida, 2000 (1)	50 F	Kidney	NA ("Thin")	9 mo	TAC + PDN + AZT	DM Controlled on SC Insulin

BMI: body-mass-index; M: male; F: female; BM: bone marrow; TAC: tacrolimus; MPL: methylprednisolone; PDL: prednisolone; PDN: prednisone; MPS: mycophenolate sodium; MMF: mycophenolate mofetil; AZT: azathioprine; CYC: cyclosporine; RG: random glucose; FG: fasting glucose; Yr: year; Mo: month; Wk: week; NA: not available; DM: diabetes mellitus; Tx: therapy

Five of the now seven reported cases detail the development of diabetic ketoacidosis at least six months after renal transplantation (2-5, 7). In contrast, our case and the case detailed by Dr. Tuğcu and his colleagues describe the presentation of DKA and new onset diabetes within three months of transplantation (6).

Maintenance immunosuppressive therapy is essential to prevent organ rejection in renal transplant recipients. Calcineurin inhibitors play an integral role in most immunosuppressive regimens, with tacrolimus being the preferred agent over cyclosporine, as several studies show lower incidence of acute rejection with its use (1). Both calcineurin inhibitors are known to cause toxicity to pancreatic islet beta cells and may also directly affect transcriptional regulation of insulin expression (5). Evidence suggests that tacrolimus causes greater incidence of severe swelling-vacuolization, endoplasmic reticulum stress and apoptosis of pancreatic islet beta cells when compared to cyclosporine (8). Tacrolimus associated diabetogenic effects threaten the health and longevity of the allograft by predisposing the recipients to microvascular and macrovascular diabetic complications which subsequently reduce allograft survival.

The development of diabetes mellitus Type 1 with ketoacidosis in patients on therapeutic tacrolimus with no risk factors for diabetes highlights the need for alternative immunosuppressive agents which won't compromise long-term survival of the patients' allograft. This case report highlights the importance of regular fasting blood glucose monitoring in patients on a tacrolimus-regimen for immunosuppression in order to prevent the life-threatening complication of diabetic ketoacidosis and subsequent allograft rejection in the setting of uncontrolled diabetes mellitus.

Post-transplant diabetes mellitus is associated with increased mortality, by approximately 10 %, among renal transplant patients. The reduction in survival rate due to post-transplant diabetes mellitus is largely due to cardiovascular disease, such as coronary artery disease and congestive heart failure (9). Given the negative impact of NODAT in the survival of renal transplant patients, preventive efforts should be made to minimize risk factors. Known risk factors for NODAT include obesity, hepatitis C, African American race, Hispanic ethnicity, family history of diabetes mellitus, use of calcineurin inhibitor and/or corticosteroid. Early identification of patients at high risk for NODAT would help tailor immunotherapeutic suppressant regimen and to aggressively manage modifiable risk factors for NODAT (10, 11). The International Diabetes Federation (IDF) recommends proactive prescreening of all post-transplant patients for NODAT, with measurement of fast plasma glucose at least once per week for first 4 weeks post-transplant. Afterwards, post-transplant patients should have fasting plasma glucose test at 3, 6, 12 months, at 1-year intervals thereafter. Glycated hemoglobin (Hemoglobin A1C) is recommended to be check at 3 months following the transplant procedure (12).

Calcineurin inhibitors, including tacrolimus and cyclosporine, inhibit calcineurin in β-cells of the pancreas. Inhibition of calcineurin indirectly suppresses expression of genes involved in insulin production. In particular, adverse glycemic effect occurs with a greater incidence with tacrolimus than cyclosporine. This is thought to be mostly due to tacrolimus-induced changes in the level of β-cell enriched transcription factors, forkhead

box protein O1 (FoxO1) and v-maf musculoaponeurotic fibrosarcoma oncogene homolog A (MafA). Tacrolimus selectively promotes nuclear translocation of FoxO1 and cytoplasmic location of MafA. These modulations of transcript factors then cause β-cell dysfunction, attributing to the development of NODAT (13).

Conclusion

Considering the potentially devastating complication of allograft compromise due to undiagnosed NODAT, it is imperative that clinicians monitor patients for signs of impaired glucose metabolism, specifically those who are treated with tacrolimus.

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