Post-Transplant Diabetic Ketoacidosis in a Liver Transplant Recipient Under Tacrolimus Immunosuppression: Role of Cholestatic Liver Enzymes in Predicting the Risk: Case Report

Takrolimus Immünsüpresyonu Alan Karaciğer Transplant Alıcısında Post-Transplant Diyabetik Ketoasidoz: Riskin Öngörülmesinde Kolestatik Karaciğer Enzimlerinin Rolü

Kendal YALÇIN,[a]
Nazım EKİN,[a]
Alpaslan TUZCU,[b]
Ramazan İDİLMAN[c]

[a]Division of Gastroenterology and Hepatology,
[b]Division of Endocrinology and Metabolism Diseases,
Dicle University Faculty of Medicine, Diyarbakır
[c]Department of Gastroenterology, Ankara University Faculty of Medicine, Ankara

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Yazışma Adresi/*Correspondence:*
Kendal YALÇIN
Dicle University Faculty of Medicine, Division of Gastroenterology and Hepatology, Diyarbakır, TÜRKİYE/TURKEY
kendalyalcin@hotmail.com

ABSTRACT We report the case of a 42-year old man who presented with severe diabetic ketoacidosis 5 months after receiving liver transplantation. The post-transplant course was otherwise unremarkable except for the occasional episode of transient hyperglycemia and increased levels of ALP and GGT at four months post-transplant. Five months post-transplant, the patient was admitted to our clinic after presenting with polyuria, polydipsia, confusion, and Kusmaull respiration. The patient developed severe diabetes mellitus with fasting blood glucose levels up to 817 mg/dl. Treatment consisted of an insulin infusion, continued intravenous fluids and antibiotics. After treatment, his hyperglycemia, acidosis, and ketosis resolved. This case report highlights the significant risk for new-onset diabetes and diabetic ketoacidosis for patients using tacrolimus for immunosuppression. Unusual features of this case include the relatively abrupt onset of severe hyperglycemia, the presentation with frank ketoacidosis, coexistance of abrupt elevation of cholestatic liver enzymes, and the persistence of insulin-dependence despite otherwise successful withdrawal of steroids. Sudden elevation of cholestatic liver enzymes should also prompt caution for diabetic emergencies in the course of post-transplant period.

Key Words: Diabetic ketoacidosis; liver transplantation; tacrolimus

ÖZET Bu yazıda 42 yaşında erkek bir hastada karaciğer naklinden 5 ay sonra şiddetli diabetik ketoasidoz gelişen bir vaka sunulmuştur. Hastanın nadir ve geçici hiperglisemi ve post-transplant 4. ayda saptanan yüksek ALP ve GGT dışında post transplant dönemi sorunsuz idi. Post-transplant 5. ayda hasta kliniğimize poliüri, polidipsi, konfüzyon ve Kusmaull solunumla başvurdu. Hastada açlık kan şekerinin 817 mg/dl'ye çıktığı şiddetli diabetes mellitus geliştiği saptandı. Hastaya insulin infüzyonu, sürekli intravenöz sıvı ve antibiyotik tedavisi uygulandı. Tedaviden sonra hastada hiperglisemi, asidoz ve ketozis bulguları düzeldi. Bu vaka, immünsüpresyon için takrolimusun kullanıldığı hastalarda yeni başlangıçlı diyabet ve diyabetik ketoasidoz bakımından yüksek riskin önemini vurgulamaktadır. Bu vakanın sıradışı özellikleri, rölatif olarak ani başlayan şiddetli hiperglisemi, açık bir ketoasidoz tablosu, aynı zamanda kolestatik karaciğer enzimlerinde ani yükselme ve başarılı bir steroid kesimine rağmen insulin bağımlığının devamı olarak sıralanabilir. Post-transplant dönemde, kolestatik karaciğer enzimlerinde ani yükselme diyabetik aciller konusunda dikkat çekmelidir.

Anahtar Kelimeler: Diyabetik ketoasidoz; karaciğer transplantasyonu; takrolimus

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For many years new-onset diabetes after transplantation has been recognized as a well-recognized complication of solid-organ transplantation, although its importance has been greatly underestimated. Studies have shown that the cumulative incidence of this condition in heart transplant recipients may reach 32% at 5 years, similar to that reported in

kidney and liver transplant patients.[1] Experimental and clinical studies have suggested that immunosuppressive agents currently used in transplantation such as the calcineurin inhibitors (cyclosporine (CsA) and tacrolimus) and steroids account for a large degree of the increased risk of these patients for developing new-onset diabetes after transplantation.[2,3]

Tacrolimus is a macrolide immunosuppressant produced by Streptomyces bacteria, which inhibits the transcription of the insulin gene by inhibition of calcineurin after binding to FK506-binding protein 12.[4,5] The mechanism of action for this drug involves suppressed humoral immunity via inhibition of T-lymphocyte activation.[4] Tacrolimus also inhibits the mRNA expression of insulin as well as cytokines and cell-surface receptors that are essential for an immune response.[4] Clinical trials have also shown tacrolimus to be as rescue therapy for acute rejection in transplant recipients.[6,7]

However, the diabetogenic potential of tacrolimus is much higher than that of cyclosporine in the early post-transplantation period.[2] Despite its excellent prophylactic effect on allograft rejection, post-transplantation diabetes mellitus (PTDM) has become a major drawback in its clinical application.[8,9]

Here, we report a case of post-transplant diabetic ketoacidosis (DKA) in a liver transplant recipient treated with tacrolimus and methylprednisolone. The purpose of this case report is to increase the awareness of physicians to this rarely reported but serious post-transplant complication and considers the role of tacrolimus as a diabetogenic agent.

CASE REPORT

A 42-year-old man had undergone living related donor transplantation (LRDT) for end-stage liver disease due to hepatitis delta virus (HDV). Prior to transplantation, he had cirrhosis of Child-Pugh class C and hepatocellular carcinoma (HCC) of Okuda stage B. He had previously diagnosis of liver cirrhosis since 1985 and had 4 sessions of variceal band ligation for prophylaxis of variceal hemorrhage and two sessions of transarterial chemoembolization for HCC. The donor was the daughter of the patient's aunt who is blood compatible with recipient. Pretransplant metabolic studies were all in normal range.

He had an uncomplicated liver transplantation. The allograft functioned immediately and subsequent laboratory tests indicated stable hepatic function. His induction immunosuppression medication consisted of tacrolimus 6 mg daily, methylprednisolone and subsequently the tacrolimus dose was adjusted to maintain trough levels of 5-10 ng/mL. The post-transplant course was otherwise unremarkable. He was on maintenance immunosuppression consisting of tacrolimus in a dose of 2 mg bid, methyl-prednisolone 10 mg daily, lamivudine 100 mg daily, hepatitis B immune globuline (HBIG) 2000 IU montly, lansoprazole 30 mg daily, prophylactic doses of trimethoprim-sulfamethoxsazole, and acyclovir.

At four months post-transplant, he developed hyperglycemia with a fasting serum glucose level of 155 mg/dL. Meanwhile, mild elevations were detected in ALT and AST levels, whereas sharp elevations in ALP and GGT levels. The initial management strategy included non-pharmacologic therapy; that is, diet modification, patient education and tapering the dose of steroid. Methylprednisolone was tapered and withdrawn at post-transplant fifth month. Except this instance, his previous serum glucose levels were all in normal range. On admission, his height was 175 cm and weight was 70.0 kg (BMI=22.8 kg/m^2). He was not obese with a body mass index of 23.4 and had no prior history of diabetes mellitus but his family history revealed that his two paternal aunts had non-insulin dependent diabetes mellitus (NIDDM).

Approximately, 5 months following transplantation, the patient was readmitted to the hospital after presenting with fatigue, polyuria, polydipsia, vomiting, confusion, visual blurring and Kussmaul respiration. The physical examination revealed an ill-appearing, uncomfortable, and tachypneic patient with a temperature of 37.1^{o}C, a heart rate of 91 beats per minute, a respiratory rate

of 22 breaths per minute, and a blood pressure of 110/65 mmHg. Physical examination also showed mild splenomegaly, a tender abdomen with normoactive bowel sounds, and operation scar of the liver transplantation in the abdomen. The patient did not seem to be jaundiced. The neurologic examination was significant for confusion, intermittent lethargy and tremor. The tone, strength, and reflexes were normal and symmetric. Pupil reflexes and funduscopic examination were otherwise normal with no finding of diabetic retinopathy.

Diagnostic evaluation included an electrocardiogram (ECG) revealed a sinusal tachycardia. A chest radiograph revealed clear lung field and a normal cardiac silhouette. His laboratory data on admission was shown in Table 1. His initial laboratory tests, revealed the leukocyte count 25100 k/ul; plasma glucose 817 mg/dL; sodium 129 mmol/l; chloride 92 mmol/l; potassium 6.8 mmol/l; creatinine 1.4 mg/dL; serum albumin 3.9 g/dL; and glycosylated haemoglobin A1c (HbA1c) level of 9.07%. His tacrolimus level was 12.1 ng/mL. Arterial blood gas analysis revealed a pH of 7.025, pCO_2 of 22.4 mm Hg, pO_2 of 48.6 mm Hg, HCO_3 of 7.5 mmol/l (22-26) and base excess -23.4 mmol/1. Serum lactate was 21 mg/dL (2.7-7.2 mg/dl) with a calculated anion gap of 23. The urine analysis revealed a specific gravity of 1.020 with +++ positivity (150 mg) for urinary ketones and +++ positivity (1000 mg) for glucose. Laboratory evaluations including liver function tests, complete blood counts, serum electrolytes, insulin, C-peptide, and HbA1c levels were performed (Table 1). The patient was diagnosed with new-onset diabetes mellitus complicating diabetic ketoacidosis.

The patient's condition was deteriorated and was admitted to the intensive care unit. Severe diabetic ketoacidosis was diagnosed and initial management consisted of an insulin infusion, continued large volumes of intravenous normal saline (500 mL/h), and sodium bicarbonate and antibiotics. A bolus of 0.1 units/kg of regular insulin was given intravenously, followed by a regular insulin drip at 0.1 units/kg/h. Plasma glucose concentrations at 4 and 6 h after initial treatment were 416 and 354 mg/dl, respectively. After 2 days, plasma glucose concentration was decreased to 189 mg/dL and his arterial blood gas (ABG) revealed pH 7.322 and urinary ketones became negative.

Thereafter, multiple subcutaneous insulin injections were started including multiple dose insulin injections four times daily (8/8/8 U regular insulin and a single injection of 12 units of intermediate-acting (NPH) insulin at bedtime) on the second day after admission. Meanwhile, he had transient bouts of hypoglycemia and for this reason the amount of insulin was reduced to 6/6/6/8 U. The dose and number of insulin injections was adjusted to achieve target glucose levels. His hyperglycemia, acidosis, and ketosis resolved. Fasting blood glucose 28 days after admission was 101 mg/dL. The plasma glucose was well-controlled and the hospital course was uneventful. One month after admission, insulin was discontinued and diabetic therapy consisted of only dietary management. After one month, his blood glucose level remained consistently in normal range, oral glucose tolerance test (OGTT) was found to be normal and no insulin resistance was detected.

A computerized tomography scan without contrast of the brain was performed. The results were normal with no findings of cerebral edema. The diminished mental status was thought to be secondary to metabolic encephalopathy. A work-up for secondary causes was unrevealing. All autoantibodies including islet beta-cells and antiglutamic acid decarboxylase (GAD) antibodies were found to be negative except for positivity for anti-thyroglobuline antibody. Total anti-delta antibody in serum was positive also with hepatitis B surface antigen, and anti-HBe antibody. Serum HBV DNA and HDV RNA was undetectable.

The immunosuppression was changed from tacrolimus plus methyl prednisolone to cyclosporine plus mycophenolate mofetil. Now, his medication is consisted of CsA (100 mg morning, 75 mg evening), mycophenolate mofetil (500 mg two times daily) together with lamivudine 100 mg daily and HBIG. He had no evidence for recurrence of HCC. There was no recurrent allograft infection with HDV in the course of patient. At last follow-

TABLE 1: Laboratory data.

Variables	PreTx 1 mo	Before Tx	Post Tx 1 mo	Post Tx 3 mo	Post Tx 3 mo	Post Tx 4 mo	Post Tx 5 mo	Post Tx 5 mo	Post Tx 5 mo	Post Tx 6 mo	Post Tx 8 mo	Post Tx 9 mo	Post Tx 12 mo	Post Tx 14 mo	Post Tx 15 mo	Post Tx 17 mo
Date	02.05.03	13.05.03	12.08.03	07.10.03	28.10.03	11.11.03	02.12.03	04.12.03	30.12.03	20.01.04	24.03.04	26.04.04	27.07.04	24.09.04	22.10.04	10.12.04
WBC (K/uL)	1670	1900	2700	3800	3200	3200	25100	2180	4790	1400	2700	2710	2500	2970	4200	4590
Neutrophil (K/uL)	1100		1900	2270	2340	2340	24400	1850	3400	700	1400	1600	1700	2020	2700	3300
Lymphocyte (K/uL)	300		450	1170	580	580	655	184	873	400	1000	835	600	679	1170	1000
Hematocrite (%)	25.4	28.5	33.2	40.9	35.3	35.3	40	25.7	35.9	32.5	36.7	38.2	40.7	38.3	38.9	37.6
Platelet (K/uL)	19300	23000	81000	62000		65000	178000	31000	46200	69000	61000	78700	59000	50700	66200	62900
ESR (mm/hour)	5		2	2	2	2	8	47	19		2	3	2	5	5	14
PTT (sec)	36.6	31.9	16.2			16.2	22.6	18.1	15.1	15	14.9	14.6	15	14.5	14.2	12.9
Glucose (mg/dL)	103	81	93	80	127	155	817	189	101	104	98	101	99	89	107	108
Creatinine (mg/dL)	0.7	0.7	1.0	0.9	1.0	0.9	1.4	1.5	1.2	1.3	1.2	1.0	1.1	1.0	1.08	1.2
Sodium (mmol/L)	140	132	134	138	137	137	129	130	138	139	135	142	137	140	138	138
Potassium (mmol/L)	3.8	4	4.5	4.4	4.6	4.6	6.8	5.8	5.2	5.0	5.3	5.2	4.6	4.8	4.8	4.8
ALT (U/L)	14	18	57	46	82	69	26	14	22	21	21	15	33	33	40	18
AST (U/L)	27	33	37	23	41	35	15	31	26	19	19	14	21	22	23	14
Albumin (g/dL)	3.1	3.1	3.6	4.0	3.8	3.8	3.9	3.2	5.1	4.8	4.6	4.4	4.7	4.5	4.6	4.6
Total bilirubin	4.6	6.6	1.7	1.9	0.9	0.9	1.6	0.7	1.3	0.9	1.1	1.0	0.8	1.0	1.58	1.1
ALP (U/L) (53-128)	78	128	124	69	217	1142	466	314	185	146	119	140	147	159	234	257
GGT (U/L) (0-50)	35	24	41	43	210	381	590	242	69	41	21	23	52	72	106	79
Kolesterol (mg/dL)	79		104	131	120	120	214	207	118	107	97	99	116	123	139	150
Tryglyceride (mg/dL)	48		130		103	103	291	328	72	83	124	135	103	108	134	161
Tacrolimus (ng/mL) (5-10)			6.2	14.2	7.4	17.5	11.2									
Cyclosporine-A (ng/mL) (100-300)										123	216	78	339	67	142	137
Insuline (uU/mL) (3-17)								39.23	4.48	5.28				8.45		9.10
C-peptide (ng/mL) (1.1-5)							<0.5	5.41	4.22	3.59				2.50		2.60
HbA1c (%) (4.5-5.7)								9.07	6.29	4.17	4.32					4.21
OGTT										Normal	Normal	Normal				Normal

Tx: Transplantation; Mo: Month.

up on post-transplant 17 months, his fasting glucose level 108 mg/dL, fasting plasma insulin level 9.10 uIU/mL, fasting plasma C-peptide 2.60 ng/mL, and HbA_{1c} 4.21%. In the period of 18 months of follow-up no episode of hyperglycemia was detected and the patient has remained well without evidence of diabetes in the long term follow-up.

DISCUSSION

We present here, a rare case of diabetes mellitus with diabetic ketoacidosis in the recipient of living related donor transplantation, at the 5th month of post-transplant period. Prior to presentation, this patient was not known to be diabetic. In pre-transplant period, the patient had HDV related end-stage liver cirrhosis coexisting with hepatocellular carcinoma. The course was transient with full recovery and no any graft complication was observed.

PTDM occurs mainly within 3 months after transplantation, since the high doses of immunosuppressive drugs are used at that period to prevent rejection. There is limited information regarding the incidence and features of PTDM in LDLT recipients. Poorly controlled hyperglycemia in PTDM may result in nonketotic hyper-osmolar coma.[8] But, DKA has only occasionally been mentioned in transplant studies of PTDM and rarely reported.[10-17] Although drugs used in liver transplant recipients such as steroids, cyclosporine, and particularly, tacrolimus have diabetogenic potential, diabetic ketoacidosis is uncommon. There are few data concerning the long-term follow-up of these patients.

The calcineurin inhibitors cyclosporine and tacrolimus are initiated at the time of transplantation and serve as the basis for most maintenance therapy. Both agents have similar toxicity profiles. However, hyperglycemia and diarrhea are more common with tacromilus and unlike most other metabolic complications, new-onset diabetes mellitus occurs more frequently with tacrolimus than with CsA.[18-20]

Traditionally, the pathophysiology of PTDM centered on insulin resistance induced by corticosteroid.[21] It is now clear that 1) calcineurin inhibitors are diabetogenic, thereby increasing the incidence of PTDM in patients who also receive steroids; and 2) tacrolimus is more potent than cyclosporine in this regard. Diabetes mellitus develops in more than one third of liver recipients post-transplant and the majority of patients are insulin-dependent.[22,23] Concomitant use of cyclosporine and tacrolimus with glucocorticoids, may further increase this risk in primary liver transplant recipients.

This previously non-diabetic patient clearly has developed post-transplant diabetes mellitus. Unusual features of this case include the relatively abrupt onset of severe hyperglycemia, the presentation with frank ketoacidosis, coexistance of abrupt elevation of cholestatic liver enzymes, and the persistence of insulin-dependence despite otherwise successful withdrawal of steroids. Although he had a family history of type 2 diabetes, there were no autoantibodies against islet beta-cells and GAD.

Initially, this patient had a mild hypergycemia, which was aimed to control by a stepwise approach similar to that recommended for patients with type 2 diabetes.[24-26] The management was consisted of lifestyle modification, patient education and reducing the dose of steroid. The dose of steroid firstly was reduced and then discontinued. Unfortunately, the patient had a progressive course and 21 days later (from the first high glucose measurement as 155 mg/dL), presented with a rapidly developed diabetic ketoacidosis, despite of initial management and discontinuation of steroids. In the course of patient, tacrolimus was stopped and CsA with mycophenylate mofetil was initiated. The patient improved progressively, his hyperglycemia disappeared and had no need for any anti-diabetic medication. It was previously, reported that changing immunosuppression from tacrolimus to cyclosporine was associated with regression of diabetes in three cases.[27,28]

On admission, he was initially treated with insulin, however, he was finally treated only with diet therapy since his insulin secretion was recovered. His plasma glucose was well-controlled by

diet therapy alone. These data suggest that the patient had PTDM rather than type 1 diabetes mellitus. Although, his serum insulin and C-peptide level was not measured at the time of admission, temporary severe beta-cell dysfunction was suggested because of her clinical course, which was improved after the treatment.

Data from kidney transplant patients suggest that risk of developing diabetes post-transplant is highest with corticosteroids; however, reducing the dose of these agents post-transplant can lessen this risk.[29,30] It is suggested that the dose of corticosteroids should therefore be reduced as soon as possible post-transplant in patients at risk of developing diabetes.[24] But in the reported case although the dose of steroid firstly was reduced and then discontinued, it did not have any effect on developing of diabetic ketoacidosis. So, this approach may not be sufficient to prevent diabetic urgencies in selected cases.

The mechanism underlying the development of diabetes with tacrolimus is unclear. The drug may produce beta cell toxicity, diminished insulin synthesis or release, and decreased peripheral insulin sensitivity.[1,31] The pathophysiology of DKA might be due to beta cell dysfunction and peripheral insulin resistance.[15] We suggest that the pathophysiology of DKA in our case may be significant degree of beta cell impairment related to the relatively high tacrolimus concentration in the absence of a triggering event. We conclude that posttransplant glucose intolerance and DKA development may be due to dose-dependent, direct effects of tacrolimus on pancreatic beta cell function, which may be controlled by dose reduction or drug cessation. We suggest that all patients undergoing liver transplantation should be screened routinely for PTDM after transplantation, and that, such patients may benefit from the avoidance of tacrolimus, as it may cause permanent beta-cell injury.

It is suggested that, tacrolimus-associated post-transplant diabetes mellitus may be more complicated, and some patients may demonstrate ketoacidosis, although it is reversible after withdrawing tacrolimus. So, we should pay more attention to glucose metabolism and risk of diabetes mellitus in patients with immunosuppressive therapy. Awareness of the subacute presentation of post-transplant diabetic ketoacidosis should confer a heightened level of suspicion upon clinicians, so that diagnostic monitoring and therapeutic strategies can be optimized. In the present case, cholestatic enzymes were concurrently increased with the development of diabetic ketoacidosis. Increased cholestatic liver enzymes may be a risk factor for the development of diabetic ketoacidosis. For this reason, sudden increases in cholestatic liver enzymes should prompt a caution for the development of diabetic ketoacidosis. Moreover, sudden elevation of cholestatic liver enzymes should also prompt caution in the course of post-transplant period. It is recommended that all potential transplant recipients receive regular monitoring of fasting plasma glucose levels pre-transplant and are screened for the risk factors that appear to predispose patients to the development of diabetes post-transplant and its severe complications.

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