

A rare but important adverse effect of tacrolimus in a heart transplant recipient: diabetic ketoacidosis

Zeynelabidin Öztürk¹, E. Nazlı Gönç², Leman Akcan¹, Selman Kesici³, İlker Ertuğrul⁴, Benan Bayrakçı³

Divisions of ²Pediatric Endocrinology, ³Pediatric Critical Care, and ⁴Pediatric Cardiology, ¹Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey. E-mail: zeynelabidin_ozturk@hotmail.com

Received: 22 October 2014, Accepted: 3 April 2015

SUMMARY: Öztürk Z, Gönç EN, Akcan L, Kesici S, Ertuğrul I, Bayrakçı B. A rare but important adverse effect of tacrolimus in a heart transplant recipient: diabetic ketoacidosis. Turk J Pediatr 2015; 57: 533-535.

Heart transplantation indications in pediatric population include congenital heart diseases, cardiomyopathies and retransplants. Cardiomyopathy is the primary indication for 11 to 17 years of age. The surveillance after transplantation is a very important issue because of both the rejection risk and the adverse effects due to medications after transplantation. Immunosuppressive agents that are commonly used after heart transplantations have several toxicities. Here we present an adolescent patient diagnosed with dilated cardiomyopathy, performed heart transplantation, treated with tacrolimus and suffered from diabetic ketoacidosis due to tacrolimus. After the diagnosis was made the appropriate fluid and insulin therapy was started immediately and ketoacidosis resolved in the first 24 hours of the therapy. The diagnosis revised as new onset diabetes mellitus after transplantation and the tacrolimus dosage titrated to therapeutic level. After glycemic control the patient discharged with rapid acting insulin, three times daily, before meals; and long acting insulin once daily at night. In ten month follow up time the insulin dosages were progressively reduced.

Key words: heart transplantation, tacrolimus, posttransplant diabetes mellitus, new onset diabetes mellitus after transplantation, diabetic ketoacidosis.

Heart transplantation indications in pediatric population include congenital heart diseases, cardiomyopathies and retransplants¹. Cardiomyopathy is the primary indication for 11 to 17 years of age¹. The surveillance after transplantation is a very important issue because of both the rejection risk and the adverse effects due to medications after transplantation². Glucocorticoids, calcineurin inhibitors, signal proliferating inhibitors, antilymphocyte antibodies and a few of other immunosuppressive agents like mycophenolate are the most commonly used drugs after heart transplantation². Several toxicities of these drugs are observed frequently. Here in we present an adolescent patient diagnosed with dilated cardiomyopathy, performed heart transplantation, treated with tacrolimus and suffered from a rare but important adverse effect of tacrolimus.

Case Report

A 17-year-old, male adolescent who was diagnosed with dilated cardiomyopathy and performed heart transplantation three months ago, referred to our hospital because of fatigue and dyspnea. In the medical history, one year after the diagnosis of upper respiratory tract infection cardiomegaly was detected in a routine chest radiogram and the diagnosis of heart failure and dilated cardiomyopathy were established, and treatment with carnitine and anti congestive therapy including digoxin, enalapril and furosemide was started. In the echocardiogram the ejection fraction was 29% and the patient was symptomatic, so heart transplantation was performed, and patient underwent immunosuppressive therapy. He had developed renal failure while treated with cyclosporine, so the therapy was changed with tacrolimus. Although he suffered from

posterior reversible encephalopathy syndrome associated with tacrolimus therapy, tacrolimus was not withdrawn because there was no other favorable immunosuppressive drug option and the patient was treated with levetiracetam. The immunosuppressive therapy after discharge included prednisolon (0.5 mg/kg; 40 mg/day), tacrolimus (0.1 mg/kg; 4 mg/day) and mycophenolate (375 mg/dose, twice daily). His mother was diagnosed with type 2 diabetes mellitus and oral antidiabetic agents were started a few months ago. There were no other significant medical features in the family history.

The patient referred to our hospital because of fatigue and dyspnea three months after transplantation. Body weight was 40 kg (<3 percentile), height was 161 cm (3-10 percentile), moon face, tachypnea (35 breaths per minute), and a sacral ulceration (3x3 cm) were present at the physical examination. The hemoglobin level was 15.7 g/dl; the white blood cell count was 12800/mm³, the chest radiogram and the electrocardiogram were normal. Brain natriuretic hormone level was 89.1 (<100) pg/ml, CK/MB level was 1.39 ng/ml (0 – 4.94); troponin T level was 0.030 ng/ml (0 – 0.014); myoglobin level was <21.0 ng/ml (28 – 72). In the echocardiogram there was no rejection finding, 1st degree mitral insufficiency and focal septal and left ventricular concentric hypertrophy were present. The blood pH was 7.22; bicarbonate concentration was 13.3 mmol/L; blood sugar level was 574 mg/dl (31.8 mmol/L), simultaneous insulin level was <2 µIU/ml. In the urine analysis, ketonuria (150 mg/dl) was present. The other metabolic tests, serum electrolyte levels and renal function tests were normal. HbA1C level was 9.7%. Anti insulin, anti islet and anti glutamic acid decarboxylase antibodies were negative. Amylase level was 64 U/L (<450). With lightening of these clinic and laboratory findings the patient was diagnosed with diabetic ketoacidosis and rejection was ruled out. The appropriate fluid and insulin therapy was started and ketoacidosis resolved in the first 24 hours of the therapy. Tacrolimus level was 45.4 ng/ml, so we thought that diabetic ketoacidosis might be due to tacrolimus toxicity. The diagnosis revised as new onset diabetes mellitus after transplantation and the tacrolimus dosage titrated to therapeutic level

(8-12 ng/ml). After glycemic control the patient discharged with rapid acting insulin, three times daily, before meals and long acting insulin once daily at night. In ten month follow-up time the insulin dosages were progressively reduced from 2 U/kg to 0.5 U/kg.

Discussion

Heart transplantation is a life-saving therapy procedure but has several risks. Each immunosuppressive agent which is used after transplantation causes many adverse effects individually. However, they are usually combined during treatment. Glucocorticoids are associated with glucose intolerance, dyslipidemia, hypertension, osteoporosis, infections, growth retardation, skin problems and many other adverse effects². Hypertension, gingival hyperplasia, hyperlipidemia, hyperglycemia and electrolyte imbalance are often observed due to calcineurin inhibitors cyclosporine and tacrolimus². Renal toxicity incidence is more than 10 percent². The neurologic effects including encephalopathy, seizures, central nervous system infections, headache, tremor and insomnia are frequently encountered with calcineurin inhibitors².

Posttransplant diabetes mellitus (PTDM) incidence is 5% in five years after pediatric heart transplantation². Tacrolimus is one of the most diabetogenic agents used after transplantation². Tacrolimus acts by reducing insulin synthesis, secretion, sensitivity and these effects are dose dependent³. High tacrolimus levels, HLA-DR mismatch, elder age, family history for diabetes mellitus are the most important risk factors for posttransplant diabetes mellitus³. Posttransplant diabetes mellitus is a serious complication as it may cause weight loss, infections, and cardiac allograft vasculopathy that is associated with increased rejection risk². Steroid use and family history of diabetes could also be considered as risk factors for our patient to develop posttransplant diabetes mellitus. But due to high levels of tacrolimus and low level of insulin in case of hyperglycemia in our patient; we thought that tacrolimus played the major role in the development of diabetes mellitus.

To our knowledge, in the literature, there is only one patient reported by Im et al.⁴ who suffered from diabetic ketoacidosis due to tacrolimus used after heart transplantation.

But this patient's serum amylase level was high and hyperglycemia was attributed to pancreatitis. In our patient serum amylase level was normal and there were no signs of pancreatitis clinically.

Tacrolimus induced diabetes mellitus is usually reversible⁵. Insulin production improves as early as four days after tacrolimus withdrawal and is completely recovered at day 7 both in vitro and in vivo⁵. Accordingly, immediately following transplantation, the withdrawal or the decrease of Tacrolimus may be considered as prevention or treatment of PTDM, although there is no evidence to support this idea in the long run⁵. Even after 2 years; thus, reducing the dose of tacrolimus by 30% within the target range has been shown to result in a 24% increase in insulin production⁶. It's more important to prevent posttransplant diabetes mellitus⁷. So, patients who have a plan for heart transplantation must be evaluated for risk factors of diabetes mellitus before the procedure and the present risk factors should be modified if possible. After transplantation the clinicians must be aware of immunosuppressive drug toxicities. Early awareness and intervention of hyperglycemia may prevent a life threatening complication of diabetic ketoacidosis. In addition, strict drug level monitoring is essential in case of a complication of drug exchange, different combinations might be debated.

In conclusion; immunosuppressive therapy after heart transplantation is critical because of both rejection risk and complications due to the therapy. To determine the appropriate drug regimen is difficult. So, the surveillance of the transplanted patients should be accomplished by a team which can overcome the possible complications.

REFERENCES

1. Herrington CS, Tsirka AE. Pediatric cardiac transplantation. *Semin Thorac Cardiovasc Surg* 2004; 16: 404-409.
2. Costanzo MR, Dipchand A, Starling R, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2010; 29: 914-956.
3. Pham PT, Pham PM, Pham SV, et al. New onset diabetes mellitus after transplantation: an overview. *Diabetes Metab Syndr Obes* 2011; 4: 175-186.
4. Im MS, Ahn HS, Cho HJ, et al. Diabetic ketoacidosis associated with acute pancreatitis in a heart transplant recipient treated with tacrolimus. *Exp Clin Transplant* 2013; 11: 72-74.
5. Prokai A, Fekete A, Pasti K, et al. The importance of different immunosuppressive regimens in the development of posttransplant diabetes mellitus. *Pediatr Diabetes* 2012; 13: 81-91.
6. van Hooff JP, Christiaans MH, van Duijnhoven EM. Evaluating mechanisms of post-transplant diabetes mellitus. *Nephrol Dial Transplant* 2004; 19: vi8-vi12.
7. Miller J, Mendez R, Pircsh JD, et al. Safety and efficacy of tacrolimus in combination with mycophenolate mofetil (MMF) in cadaveric renal transplant recipients. FK506/MMF dose-ranging kidney transplant study group. *Transplantation* 2000; 15: 875-880.