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A Case of New Onset Diabetes Mellitus in the Long-Term After Kidney Transplantation

Geç Dönemde NODAT Gelişen Renal Transplantasyonlu Olgu

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ABSTRACT

Diabetes which first appears after transplantation is called New Onset Diabetes Mellitus after Transplantation (NODAT). NODAT is associated with increased morbidity and mortality and decreased allograft survival. Risk factors for NODAT are age older than 40 to 45 years, African and Asian ethnicity, presence of polycystic renal disease, impaired glucose tolerance before transplantation, HLA mismatches between recipients and donors, obesity, sedentary life, presence of metabolic syndrome, infection with viruses such as cytomegalovirus (CMV) and hepatitis C virus (HCV), immunosuppressive therapy including corticosteroids for acute rejection, and calcineurin inhibitors.

NODAT often appears in the first years of transplantation. It may be mainly because high doses of steroids and calcineurin inhibitors are used. In this report, a case of NODAT associated with tacrolimus, occurring four years after cadaveric kidney transplantation and successfully treated by switching from tacrolimus to cyclosporine will be presented.

KEY WORDS: Cyclosporine, Kidney transplantation, NODAT, Tacrolimus

ÖZ

Transplantasyondan sonra ilk kez ortaya çıkan diyabet "New Onset Diabetes Mellitus after Transplantation (NODAT)" olarak tanımlanır. NODAT artmış mortalite ve morbidite ile azalmış allograft sağ kalımı ile ilişkilidir. Transplantasyon hastalarında NODAT için risk faktörleri; 40-45 yaş üstü, Afrika ve Asya ırkından olmak, etiyolojide erişkin polikistik böbrek hastalığı varlığı, daha önceden kan şeker regülasyonunun bozuk olması, donör ve alıcı arasında HLA uyumsuzluğu olması, obezite, sedanter yaşam, metabolik sendrom varlığı, HCV ve CMV gibi virüsler, akut rejeksiyon tedavisinde kullanılan kortikosteroidler ve kalsinörin inhibitörleri gibi ilaçlar gösterilmiştir.

NODAT sıklıkla transplantasyonun ilk yıllarında ortaya çıkar. Bunun başlıca sebebi ise kullanılan steroid ve kalsinörin inhibitörlerinin yüksek dozda kullanılmasıdır. Biz böbrek naklinin dördüncü yılında geç dönemde NODAT gelişen, takrolimus tedavisinden siklosporine geçtiğimiz renal nakilli hastamızda başarılı tedavi tecrübemizi sunuyoruz.

ANAHTAR SÖZCÜKLER: NODAT, Renal transplantasyon, Siklosporin, Takrolimus

INTRODUCTION

Diabetes which first appears after transplantation is called New Onset Diabetes Mellitus after Transplantation (NODAT). The incidence of NODAT is 7%-46%. About 1/3 of renal transplant recipients have impaired blood glucose regulation within the first six months of transplantation. New Onset Diabetes Mellitus after Transplantation is associated with increased morbidity and mortality and decreased allograft survival (1-3).

The condition can be diagnosed at any time after transplantation by the presence of the following symptoms and laboratory results: polydipsia, polyuria and weight loss, blood glucose concentrations of ≥200 mg/dL (11.1 mmol/L) measured at any time, blood

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glucose concentrations of >126 mg/dl (7.0 mmol/L) measured after an eight-hour fast or two-hour blood glucose concentrations of ≥200 mg/dL (11.1 mmol/L) measured through an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization (WHO), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. It can be diagnosed by fasting blood glucose concentrations between 100 and 125 mg/dL (5.6 and 6.9 mmol/L) or two-hour blood glucose concentrations between 140 and 199 mg/dL (7.8 and 11.0 mmol/L) measured through an oral glucose tolerance test according to the American Diabetes Association (ADA) guidelines (4).

Risk factors for NODAT are age older than 40 to 45 years, African and Asian ethnicity, presence of polycystic renal disease, impaired glucose tolerance before transplantation, HLA mismatches between recipients and donors, obesity (defined as BMI greater than 30 kg/m^2), sedentary life, presence of metabolic syndrome, infection with viruses such as cytomegalovirus (CMV) and hepatitis C virus (HCV), immunosuppressive therapy including corticosteroids for acute rejection, calcineurin inhibitors, m-TOR inhibitors such as sirolimus, family history of diabetes among first-degree relatives, recipients of deceased donor kidneys, male recipients and male donors (5-9).

New Onset Diabetes Mellitus after Transplantation often appears within the first years of transplantation (10). In this report, a case of NODAT associated with tacrolimus, occurring four years after cadaveric kidney transplantation and successfully treated by switching from tacrolimus to cyclosporine will be presented.

CASE

A forty-one year old male patient undergoing a cadaveric renal transplantation four years ago presented to our outpatient clinic with dry mouth, polydipsia, polyuria and weakness. The patient was on treatment with prednisolone 5 mg/day, tacrolimus 1,5 mg/day and mycophenolate sodium 1440 mg/day. He did not have a family history of diabetes. On physical examination, his vital signs were normal (blood pressure: 120/85 mm hg, heart rate: 72/ min.) and he did not have any pathological signs except for dry mouth. The body mass index (BMI) was 30 kg/m^2.

Results of the laboratory investigations on admission were as follows: Hb:15.4 g/ dl, htc: 46%, WBC: 7300,PLT: 218.000, blood fasting glucose: 451 mg/ dl, blood urea nitrogen: 43 mg/ dl, creatinine: 1.2 mg/ dl, , ALT: 18 U/L , Na: 135 mmol/ L, K: 4.17 mEq/L, C-reactive protein: <5 nmol/L, tacrolimus blood concentration: 4 ng/ml, and Hb A1c: 11. Arterial blood pH was 7.36 (NR: 7.35-7.44), partial carbon dioxide pressure 40 mmHg (NR: 36-43 mmHg), and bicarbonate (HCO3) 23 mEg/L (NR: 20-26 mEg/L). Results of the urinalysis were as follows: urine density 1020, PH 5, glucose 4+, no ketones, one erythrocyte and one leukocyte. Creatinine was at basal levels. Tests for HBsAg, Anti HCV, and CMV were negative. Anti-GAD and anti islet-cell antibody tests were negative.

The patient did not have diabetes before transplantation and had normal blood glucose concentrations at outpatient clinic visits for four years after transplantation. He was hospitalized in the transplant clinic with a diagnosis of NODAT. Initial treatment of NODAT comprised an intravenous saline and insulin infusion to decrease the serum glucose level. After treatment of hyperglycemia with an insulin infusion, the treatment was switched to intensive subcutaneous insulin injections 4 times a day. Despite intensive insulin treatment, he had high blood glucose levels. Tacrolimus was replaced by cyclosporine, which is a less diabetogenic agent. On the sixth day after admission, the patient's insulin needs decreased as a result of the change in his treatment and insulin was decreased to two times daily. He was discharged on day 12 with a single dose of basal insulin per day and repaglinide tablets. One week later, basal insulin was discontinued and oral antidiabetics and a diabetic diet were used. The patient's renal functions returned to basal levels.

DISCUSSION

New Onset Diabetes Mellitus after Transplantation often appears in the first years of transplantation. The incidence of NODAT varies and it has been reported to be between 30% and 37% within one year of transplantation. It may be mainly because high doses of steroids and calcineurin inhibitors are used (10). To the best of our knowledge, there has been only one case of NODAT developing long after renal transplantation (11).

Corticosteroids impair blood glucose regulation by increasing gluconeogenesis and insulin resistance, by decreasing glycogen production and insulin release and by damaging pancreatic beta cell functions (12). Calcineurin inhibitors decrease glucose intake, insulin release and insulin gene expression and cause reversible damage to pancreatic beta cells (13, 14). Tacrolimus has been reported to be more diabetogenic. Blood tacrolimus concentrations of over 15 ng/ ml are associated with a high risk of diabetes (15). The case reported here was on treatment with corticosteroids 5 mg/day and tacrolimus 1.5 mg/day when he presented. His blood tacrolimus concentration was 4 ng/ml, which is in the target range.

Patients diagnosed as NODAT are recommended to change their life-style, exercise and follow a diet. Medical treatment includes oral antidiabetics and insulin. In addition, the steroid dose is reduced and tacrolimus is replaced by cyclosporine or m-TOR inhibitors to avoid risk of rejection (16, 17). Several studies have shown that a change in medications can be useful in liver and renal transplant recipients (5, 18). Although it has been reported in the literature that cyclosporine is less diabetogenic and that there can be changes in medications, this subject is still debatable. There is no agreement on using cyclosporine instead of tacrolimus in patients diagnosed as NODAT (19, 20).

Several studies have shown the effects of insulin treatment on regeneration of beta cells (21, 22). In the present case, intensive insulin treatment did not achieve regulation of blood glucose levels. However, initiation of cyclosporine on the sixth day of admission helped regulate blood glucose levels. In a study by Hirano et al., insulin secretion and glucose intolerance were impaired and pancreatic insulin levels decreased in the rats administered FK506 1 mg/kg/day, 5 mg/kg/day and 10 mg/kg/day for 14 days. On histopathological examination, vacuolization was detected in the Langerhans islets in the rats given 10 mg/kg/day. Two weeks after cessation of the drug, pancreatic functions and morphology returned to normal (23). This suggests that the effects of tacrolimus can be reversed in a short time. In the case presented here, regulation of blood sugar levels on the sixth day after admission can be attributed to the termination of beta cell damage caused by tacrolimus rather than regeneration of beta cells due to intensive insulin treatment since it is not possible for insulin treatment to exert its effects at this early stage.

It has been noted in the literature that tacrolimus has been replaced by cyclosporine for the treatment of NODAT developing early after renal transplantation. However, there are limited data about treatment for NODAT developing late after transplantation since the incidence of NODAT is low due to lowered doses of immunosuppressants in that period. In the case presented here, NODAT was diagnosed in the fourth year after transplantation, and blood glucose regulation was achieved by replacing tacrolimus with cyclosporine without decreasing immunosuppressants and the allograft functions were not impaired at all.

In the light of our experiences with this case and the relevant literature, it can be suggested that patients developing NODAT in the early or late period after transplantation can have tacrolimus-related diabetes and that tacrolimus can be replaced by cyclosporine. This seems to eliminate diabetes or bring it under control easily and decrease the risk of diabetes-related morbidity and mortality.

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