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Case report

Diabetic Hyperosmalar State Caused by Tacrolimus in a Renal Transplant Patient: A Case Report

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Abstract

We report a 40-year-old man who presented with hyperosmolar hyperglycemic state (HHS) after receiving kidney transplant. He was treated with prednisolone and tacrolimus regimen. Three months after transplantation he was admitted to our hospital for investigation of weakness, fatigue and loss of appetite. Physical examination was unremarkable except for signs of dehydration. He was found to have severe hyperglycemia (1262 mg/ dL), mild ketosis and mild metabolic acidosis (pH 7.30), although he had not been diagnosed as diabetes mellitus. Measured effective plasma osmolality was 322 mOsm/kg. He was treated with insulin which was later stopped while diet alone successfully regulated serum glucose level. He had no family history of type 2 diabetes. Although tacrolimus has been reported to cause diabetes mellitus, the present case suggests that it may cause acute complications without previous history of diabetes mellitus. This side effect may be secondary to relative beta cell dysfunction, peripheral insulin resistance, or a combination of both.

Introduction

In various transplantation therapies, many different immunosuppressants have been used. Tacrolimus has been known to cause numerous side-effects including neuro- and nephrotoxicities [1]. In solid-organ transplantations it has been reported that tacrolimus is responsible for post-transplantation diabetes mellitus (PTDM). Hyperglycemic hyperosmolar state (HHS) is an acute complication mostly occurring in elderly type 2 diabetic patients. He-rein we have described the case of a male renal transplant recipient who had no diabetes history and developed diabetic hyperosmalar state apparently related to tacrolimus.

Case report

We report a case of a 40-year-old Caucasian man who was first diagnosed with chronic interstitial nephritis in 2003 which led to end-stage renal disease and initiation of hemodialysis therapy. There was no diabetes mellitus (DM) in his personal or family history. Four years later he underwent living-donor kidney transplantation. He had been stable under an immunosuppressive regimen of tacrolimus (4 mg/day), mycofenolate mofetil (MMF), and prednisolone (15mg/day) but three months after transplantation he was admitted to our hospital for investigation of weakness, fatigue and loss of appetite.

Initial physical examination was unremarkable except for signs of dehydration. His tongue was dehydrated and skin turgor was decreased. The patient was in mild distress, but alert and oriented. Vital signs were as follows: axillary temperature 37.3°C, blood pressure 110/70 mmHg, heart rate 98 beats/min, and respiration rate 18 breaths/ min. His weight was 45 kg.

Laboratory values at admission were consistent with hyperosmolar hyperglycemic state (HHS). Measured effective plasma osmolality was 322 mOsm/kg. Complete blood count values were as follows: white blood cell count 12100/mm^3, hemoglobin 11.9 g/dL, hematocrit 34%, and platelets 219000/µL. Basic serum levels of biochemical parameters were as follows: sodium 126 mEq/L, potassium 5.88 mEq/L, blood urea nitrogen 66 mg/dL, creatinine 3.2 mg/dL, blood glucose 1262 mg/dL, albumin 3.01g/dL, total protein 5.8 g/dL, total bilirubin 0.36 mg/dL, calcium 8.1 mg/dL and phosphorus 7.04 mg/dL. Urinalysis showed glucosuria and mild ketonuria. Arterial blood gas analysis revealed a pH of 7.30, Pco_2 of 24 mmHg and bicarbonate (HCO_3^-) of 15 mEq/L. Results of both chest and neck radiography were normal. Serum tacrolimus level was within normal range. The last visit was 12 days ago. At the time, serum glucose level was 107 mg/dL, urinary glucose was negative, urinary output was 2500-3000 mL/day and fluid intake was 3000-3500 mL/day. Additionally, the patient was not using any diuretics.

The patient was admitted to the ICU for new-onset diabetes mellitus with hyperglycemic hyperosmolar state (HHS). Shortly after initiation of saline and regular insulin drip, his blood glucose decreased below 300 mg/

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dL. Tacrolimus was switched to cyclosporine (200 mg/day) and instead of regular insulin, premixed insulin (70% NPH and 30% regular) 36 U/day was initiated. Over the next few days he showed rapid and progressive improvement. Premixed insulin doses were tapered and discontinued. With diabetic diet he recovered fully and was discharged home at day 35. He had no further hyperglycemic symptoms or signs when he was seen at his follow up at the seventh day of his discharge.

Discussion

PTDM is a common complication of solid organ transplantation and is most commonly associated with tacrolimus (TAC) and steroid therapy. Posttransplant diabetes occurs in 2% to 53% of renal transplant recipients. Its clinical presentation ranges from asymptomatic hyperglycemia to hyperosmolar dehydration or diabetic ketoacidosis [2,3].

Tacrolimus and steroids increase insulin resistance and hepatic glyconeogenesis, favoring the development of PTDM [4]. Experimental data have shown that tacrolimus reduces insulin secretion, with deficient insulin mRNA transcription, which is probably mediated by FKBP-12 protein ligand and calcineurin inhibition of pancreatic β cells [4,5]. PTDM shows a multifactorial etiology, associated with β -cell toxicity and increased insulin resistance [6-9]. A greater incidence of PTDM has been reported among older renal transplant recipients, and those receiving steroids and tacrolimus [10]. Other risk factors include familial history of diabetes, genetic predisposition, race (African Americans and Hispanics), male gender, chronic hepatitis C infection, obesity, use of β –blockers, presence of HLADR13 and high levels of tacrolimus in the early posttransplant period [6-9,11,12].

Diabetic ketoacidosis (DKA) and the hyperglycemic hyperosmolar state (HHS) are acute metabolic complications of diabetes that are potentially fatal and require prompt, informed medical attention for successful treatment. HHS is less common than DKA, accounting for less than 1% of all diabetes related admissions, but has a much higher mortality rate, currently on the order of 11% in the US but exceeding 40% in some series, in comparison to less than 5% in DKA patients [13]. Both DKA and HHS are characterized by absolute or relative insulin deficiency and while they are usually considered separately, they represent different sites on a continuum of hyperglycemic medical emergencies. They are separated clinically by the more severe hyperglycemia and lack of appreciable ketosis or acidosis in HHS [14]. While the pathogenesis of DKA and HHS are similar, they differ in that with HHS there is greater dehydration, sufficient insulin to prevent excessive lipolysis (suppression of lipolysis requires one-tenth the amount of insulin necessary to promote glucose uptake), and counterregulatory hormones are variable and there is no clear difference between DKA and HHS [13-18].

There are several reported cases of post-transplant diabetic ketoacidosis [19-23]. There are even fewer reports on hyperglycemic hyperosmolar state after renal transplantation [24,25]. The clinical picture of our patient was attributed to tacrolimus because of the lack of the risk factors for PTDM mentioned above. Beyond that, stopping tacrolimus and substituting it with cyclosporine resulted in normal blood glucose levels without the need for insulin.

Conclusions

Rates of diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome after renal transplantation were substantially higher than reported for the general population and appear to be increasing significantly over time. In addition, there is confirmed association of both diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome with increased mortality after renal transplantation. Post transplant patients receiving tacrolimus should be followed up carefully for high blood glucose.

Conflict of interest statement. None declared.

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