March 2011

Diabetic ketoacidosis associated with tacrolimus in solid organ transplant recipients

Muhammad Qamar Masood
Aga Khan University

Madiha Rabbani
Aga Khan University

Wasim Jafri
Aga Khan University

Manal Habib
Aga Khan University

Taimur Saleem
Aga Khan University

Case Report

Diabetic ketoacidosis associated with tacrolimus in solid organ transplant recipients

Muhammad Qamar Masood,[1] Madiha Rabbani,[2] Wasim Jafri,[3] Manal Habib,[4] Taimur Saleem[5]

Section of Endocrinology, Department of Medicine,[1] Medical Graduates of Class of 2009,[2,4,5]

Section of Gastroenterology, Department of Medicine,[3] Aga Khan University, Karachi, Pakistan.

Abstract

Diabetic ketoacidosis in patients receiving tacrolimus in the post-transplant setting is rare. We describe two such cases in solid-organ transplant recipients. The first patient, a 17-year-old male, presented with severe diabetic ketoacidosis and was managed with intravenous fluids and insulin infusion. He was a known case of Laurence-Moon-Bardet-Biedl syndrome and had received a renal transplant 2 years ago and was receiving tacrolimus since then. Although diabetic ketoacidosis resolved in 24 hours, large doses of subcutaneous insulin (upto 130 units per day) were needed to keep serum glucose within the normal range. Substitution of tacrolimus with cyclosporine obviated the need for insulin or oral hypoglycaemics. The second patient, a 55-year-old woman, presented with a history of polyuria for 3 days. She had received a hepatic transplant 2 years ago and tacrolimus was being used since then. Mild diabetic ketoacidosis was managed with fluid resuscitation and subcutaneous insulin. Her insulin requirement after an uneventful recovery has been 54 - 70 units per day. Clinicians should be cognizant of the possibility of hyperglycaemic crisis presenting as sudden onset of diabetic ketocidosis in patients receiving tacrolimus. Use of an alternative calcineurin inhibitor may provide a safer solution to minimize future morbidity in such patients.

Keywords: Tacrolimus, Post Transplantation Diabetes mellitus, Diabetic ketocidosis, New onset Diabetes Mellitus.

Introduction

Diabetic ketoacidosis (DKA) is a life-threatening hyperglycaemic emergency in diabetic patients. Tacrolimus, an immunomodulator also known as FK506, is a macrolide antibiotic that has been used in the treatment of inflammatory bowel disease (IBD), atopic dermatitis, primary sclerosing cholangitis, autoimmune enteropathy as well as for the prevention of allograft rejection in liver, kidney and other solid organ transplant recipients.[1] Tacrolimus has been associated with post-transplant diabetes mellitus (PTDM). It inhibits the transcription of the insulin gene in the beta-cell via inhibition of calcineurin after binding to FK506-binding protein 12 (FKBP12).[2]

However, despite this potential, the occurrence of DKA in patients receiving tacrolimus in the post-transplant setting is rare and only a few cases of this clinical phenomenon have been reported in literature.[3,4] We describe two cases of DKA associated with tacrolimus treatment in solid-organ transplant recipients.

Case History

Case-1:

A 17-year-old boy presented with a history of polyuria, nocturia, dry mouth, and poor appetite intractable vomiting, altered mentality and irritability for one day. Although impaired fasting glucose (IFG) had been documented on a few prior occasions, overt diabetes had never been present. The patient was a known case of Laurence-Moon-Bardet-Biedl syndrome. Deterioration in kidney function was noted at the age of 12 years. This had gradually progressed to end stage renal disease (ESRD) leading to pre-emptive renal transplantation one year prior to this presentation. He had been receiving immunosuppressive treatment in the form of tacrolimus (6 mg bid), mycophenolate mofetil (1gram bid) and prednisolone (5 mg qd) in the post-transplant setting. Physical examination showed moderate to severe dehydration and confusion without any overt focus of infection. He was afebrile, had a heart rate of 140 beats per minute, blood pressure of 126/70 mm Hg, respiratory rate of 30 per minute and oxygen saturation of 94% on room air. His physical exam was significant for marked obesity, acanthosis nigricans, vision limited to light perception only, polydactyly and absence of secondary sexual characteristics. His random blood glucose was 702 mg/dl with large ketonuria and high anion gap metabolic acidosis (pH-7.1, anion gap 25 mEq/l, serum bicarbonate 06 mEq/l). The patient was managed with intravenous fluids, insulin infusion and potassium replacement as per standard protocols. Insulin infusion was discontinued within 24 hours with the normalization of arterial pH, serum anion gap and disappearance of urine ketones. However, large doses of subcutaneous insulin (up to 130 units per day) were

still needed to keep serum glucose within normal range. In view of extremely high daily insulin requirements, tacrolimus was substituted with cyclosporine A. Following this regime modification, his insulin requirements significantly reduced (40 units per day). Complete insulin independence was achieved within 2 weeks. At 2 years follow-up, serum fasting plasma glucose (FPG) levels have remained within normal range. Anti-GAD and islet cell antibodies were both negative in this patient. Serum insulin levels and C-peptide levels were, however, not checked.

Case-2:

A 55-year-old Pakistani woman presented with complaints of dizziness and polyuria for 3 days. Her past history was significant for hepatitis C virus (HCV) infection (genotype 3a) 8 years ago. Although the infection was successfully managed initially with interferon and ribavirin, it relapsed after 2 years. Development of advanced cirrhosis was associated with multiple episodes of decompensation that necessitated hepatic transplantation from China 2 years ago. She received immunosuppression in the post-transplant setting in the form of mycophenolate mofetil and tacrolimus. About 1 year after the transplant, she was still PCR positive for HCV. She received another course of interferon therapy and has been PCR negative since then. She was started on prednisolone 40 mg about 5 weeks prior to this episode for chronic rejection on liver biopsy done for raised liver enzymes. She was self monitoring her blood glucose at home; the measurements were within normal range until one week prior to presentation. Physical examination of the patient was remarkable for mild dehydration. Her FPG was 404 mg/dl and random blood glucose was 474 mg/dl with moderate ketonuria and mild anion gap metabolic acidosis (anion gap 15 mmol/l, serum bicarbonate of 16.4 mEq/l). Serum HbA1c level was 8.9%. The patient was managed with fluid replacement and subcutaneous insulin because of her stable condition. Arterial pH and serum anion gap normalized shortly and urine ketones disappeared within 12 hours. Her insulin requirement after an uneventful recovery has been 54 - 70 units per day. Her most recent FPG was 118 mg/dl. Although she is currently receiving tacrolimus and prednisolone; substitution of tacrolimus with another agent is under consideration.

Discussion

The diagnosis of drug induced diabetes mellitus (DM) in our first patient presented a diagnostic dilemma because of consideration for competing etiologies including DM secondary to Laurence-Moon-Bardet-Biedl syndrome and ketosis-prone type 2 DM. Laurence-Moon-Bardet-Biedl syndrome is an autosomal recessive condition characterized by rod-cone dystrophy, postaxial polydactyly, central obesity, mental retardation, hypogonadism, and renal dysfunction. In a large series of 109 patients, non-insulin dependent DM (NIDDM) was described in 6% of the patients.[5] In recent years, an increasing number of DKA cases have also been reported in children, adolescents and adults without any precipitating cause; these have been referred to as atypical diabetes or ketosis-prone type 2 DM. Increasing evidence indicates that this subtype of diabetes accounts for more than half of newly diagnosed black and Hispanic patients with DKA. These patients are usually obese, have a strong family history of diabetes, have a low prevalence of autoimmune markers, and lack a genetic association with HLA.[6] While our patient was obese and had negative autoimmune markers, he also did not have a family history of DM. A diagnosis of drug induced DM leading to DKA is the most likely etiology in our patient because of the rapid decline in insulin requirement and insulin independence after withdrawal of tacrolimus.

Our second patient had received a hepatic transplant secondary to HCV-induced cirrhosis. Although her infection was active after the transplant, a course of interferon was administered successfully and she had become PCR negative. She was receiving tacrolimus for about 2 years; and prednisolone was started 5 weeks before presentation, her blood sugars were monitored at home and remained in normal range on this dose for next 4 weeks, when she had this episode of hyperglycaemia culminating in DKA. In a large series comprising 21,489 primary transplant recipients in the United States, it was seen that diabetic ketoacidosis developed in 0.015% of the patients by 3 years post-transplant. Multivariate analysis showed that use of tacrolimus as well as HCV infection increased the risk of complications from new-onset DM (NODM) in these patients including DKA.[7]

Although the mechanism by which tacrolimus causes PTDM has been postulated, the reason why only certain individuals develop DKA remains unknown. There are only a handful of reports of DKA associated with tacrolimus in the literature which makes risk stratification for this rare clinical phenomenon an unfeasible task at the moment. Documentation of more cases of similar nature is, however, important.

In summary, use of tacrolimus may represent a modifiable risk factor for non-insulin dependent DM or its complications in solid organ transplant recipients.[7] Although it is a highly effective immunosuppressive agent in the post-transplant setting, the high incidence of PTDM may prove counter-productive to its prophylactic effect on allograft rejection.[8] Studies have shown that the diabetogenic potential of tacrolimus is

higher than that of cyclosporine.[9]

Conclusion

Although rare, the sporadic reports of the incidence of DKA complicating the course of PTDM in patients on tacrolimus merit consideration while selecting an immunosuppressive agent. Cyclosporine can be an effective alternative in such situations. Also, while attention is largely focused on the correction of metabolic and endocrine derangements in the acute setting in a patient presenting with DKA, clinicians should also be cognizant of the importance of seeking an underlying etiology of the disorder in order to prevent recurrent episodes in the future. If drug-induced, discontinuation of the drug offers a simple solution to minimize future morbidity.

Conflict of Interest:

The authors declare that they have no conflict of interest.

References

1. Van Dieren JM, Kuipers EJ, Samsom JN, Nieuwenhuis EE, van der Woude CJ. Revisiting the immunomodulators tacrolimus, methotrexate, and mycophenolate mofetil: their mechanisms of action and role in the treatment of IBD. Inflamm Bowel Dis 2006; 12: 311-27.
2. Tamura K, Fujimura T, Tsutsumi T, Nakarmura K, Ogawa T, Atumaru C, et al. Transcriptional inhibition of insulin by FK506 and possible involvement of FK506 binding protein-12 in pancreatic beta-cell. Transplantation 1995; 59: 1606-13.
3. Toyonaga T, Kondo T, Miyamura N, Sekigami T, Sonoda K, Kodama S, et al. Sudden onset of diabetes with ketoacidosis in a patient treated with FK506/tacrolimus. Diabetes Res Clin Pract 2002; 56: 13-8.
4. Ersoy A, Ersoy C, Tekce H, Yavascaoglu I, Dilek K. Diabetic ketoacidosis following development of de novo diabetes in renal transplant recipient associated with tacrolimus. Transplant Proc 2004; 36: 1407-10.
5. Beales PL, Elcioglu N, Woolf AS, Parker D, Flinter FA. New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. J Med Genet 1999; 36: 437-46.
6. Umpierrez GE, Smiley D, Kitabchi AE. Narrative review: ketosis-prone type 2 diabetes mellitus. Ann Intern Med 2006; 144: 350-7.
7. Burroughs TE, Swindle J, Takemoto S, Lentine KL, Machnicki G, et al. Diabetic complications associated with new-onset diabetes mellitus in renal transplant recipients. Transplantation 2007; 83: 1027-34.
8. Cho YM, Park KS, Jung HS, Joen HJ, Ahn C, Ha J, et al. High incidence of tacrolimus-associated post transplantation diabetes in the Korean renal allograft recipients according to American Diabetes Association criteria. Diabetes Care 2003; 26: 1123-8.
9. Montori VM, Basu A, Erwin PJ, Velosa JA, Gabriel SE, Kudva YC. Posttransplantation diabetes: a systematic review of the literature. Diabetes Care 2002; 25: 583-92.