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Tacrolimus-Induced Salt Losing Nephropathy Resolved After Conversion to Everolimus

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Tacrolimus is one of the most commonly used immunosuppressive drugs but tacrolimus-induced severe symptomatic hyponatremia is not a well-documented issue in kidney transplant patients.[1-4] In our current report, we describe a case of tacrolimus-induced hyponatremia in a living donor kidney recipient in whom any other potential cause of hyponatremia was excluded, and tacrolimus-induced salt losing nephropathy was resolved after conversion to everolimus.

CASE REPORT

A 44-year-old male patient who received kidney transplantation in June 2014 from his elder sister admitted to emergency unit of Baskent University Ankara Hospital on December 16 with complaints of anorexia, nausea, vomiting, and headache. He had a serum creatinine level of 1.26 mg/dL and a blood urea nitrogen level of 21 mg/dL. He was found to have severe hyponatremia with a serum sodium of 102 mmol/L and a moderately low potassium level of 3.1 mmol/L. He was receiving losartan 100 mg/day and karvedilol 25 mg/day for hypertensive treatment and triple immunosuppressive regimen of tacrolimus 2 mg/day, mycophenolate mofetil 1000 mg/day, and prednisolone 5 mg/day. In thyroid function tests, serum osmolality was in the normal range, and this was his very first hyponatremic state after the successful kidney transplantation. He was not receiving any drugs that might result hyponatremia, such as diuretics or parenteral fluids. His blood glucose level was 107 mg/dL, and he had no sign of osmotic diuresis. Twenty-four–hour urinary sodium excretion was 380 mmol/L, suggesting a salt-losing nephropathy. He received 3% hypertonic NaCl 300 mL/day, but serum sodium level only improved to 117 mmol/L after 48 hours. We suspected tacrolimus to be responsible for the salt-losing state of the recipient and discontinued tacrolimus and initiated everolimus 0.75 mg/12 hours. Forty-eight hours after discontinuation of tacrolimus, his serum sodium level improved to 132 mmol/dL with no need of more hypertonic fluid replacement. Repeated 24-hour sodium excretion was 120 mmol/day. A mild increase of serum creatinine level of 1.42 mg/dL was observed after conversion to everolimus, and all the symptoms due to hyponatremia were resolved. During 2 months of follow-up after cessation of tacrolimus, the serum sodium levels of our patient remained in the normal range, which showed that the delayed effect of hypertonic saline and volume contraction was not responsible for resolving of the hyponatremic state.

DISCUSSION

There are only few studies reporting tacrolimus-induced salt-losing state after solid organ transplantation. Higgins et al[3] showed that patients on tacrolimus were more prone to hyponatremia compared to patients receiving cyclosporine. The patients who developed hyponatremia were not attributed to any cause other than tacrolimus, but the median time was 18 days after transplantation. In our case, the patient developed tacrolimus-induced symptomatic hyponatremia 154 days after transplantation and the tacrolimus level was in the target range (5.3 ng/mL). Our patient had a urine output of 1.5 to 2.8 L/day, which excludes hyponatremia according to posttransplant polyuria. Other suspicious factors, such as hyperglycemia, hypothyroidism, use of diuretics, parenteral hypotonic fluid administration, or any drug other than tacrolimus that might cause hyponatremia, were all excluded.[1-5]

Tacrolimus is suggested to effect distal tubular Na-K-2Cl cotransporter, which may result to salt-losing nephropathy resistant to aldosterone. Therefore, fludrocortisone was reported to be effective in tacrolimus-induced nephropathy.[6] We are not able to report the response to fludrocortisone in our patient because we decided to discontinue tacrolimus and convert to everolimus to eliminate the effect of tacrolimus.

CONCLUSIONS

Tubular dysfunction and calcineurin inhibitor toxicity may develop even in the target doses of tacrolimus, and

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resistant symptomatic hyponatremic state in a transplant patient receiving tacrolimus must be considered in differential diagnosis of severe hyponatremia. Conversion to everolimus in tacrolimus-induced hyponatremia may be a good alternative immunosuppressive regimen in kidney transplant recipients with salt-losing state.[7,8]

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