Case Report

Symptomatic Hyponatremia due to Tacrolimus-Induced Salt-Losing Nephropathy in a Kidney Transplant Recipient

Abstract

Tacrolimus is the most important drug in current posttransplant immunosuppressive protocol. Salt-losing nephropathy causing symptomatic hyponatremia as an adverse effect of tacrolimus has been rarely reported. We report recurrent hyponatremia and graft dysfunction in a young renal transplant recipient, with no evidence of rejection, attributable to. tacrolimus-induced salt-wasting nephropathy.

Keywords: *Calcineurin toxicity, kidney transplant, salt-losing nephropathy, tacrolimus-induced hyponatremia*

Naveen K. K. L.[1], Prashant G. Kedlaya[1], Ananthram Jairam[1], Renuka S.[1]

[1]Department of Nephrology, St. John's Medical College Hospital, Bengaluru, Karnataka, India

Corresponding author:
Dr. Naveen K. K. L., No. 105 Nirmala Block, St John's Medical College Hospital, Koramangala, Sarjapur Road, Bengaluru - 560 034, Karnataka, India.
E-mail: naveenkumark.l.25@gmail.com

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Introduction

Tacrolimus is the backbone of immunosuppression for successful renal transplant and has become the standard of care today. Salt-losing nephropathy from the graft as an adverse effect of tacrolimus is rarely seen and restricted to case reports. Here, we report a case of recurrent hyponatremia in a young renal transplant recipient due to tacrolimus-induced salt-losing nephropathy.

Case Report

An 18-year-old lady with end-stage renal disease due to chronic interstitial nephritis was on chronic ambulatory peritoneal dialysis for 2 years, after which she underwent live related renal transplant with mother as donor in December 2019. In her pretransplant course, there were no episodes of hyponatremia. Her immunosuppressive protocol included basiliximab induction, tacrolimus 0.1 mg/kg, mycophenolate mofetil 600 mg/m^2, and steroids. Nadir serum creatinine was 0.8 mg/dl by day 5. Turbid urine was observed on day 7, and culture revealed *Escherichia coli*. She received injection meropenem; however, pyuria persisted, with repeat urine cultures growing *Candida tropicalis*. She was given intravenous (IV) liposomal amphotericin B. Her serum creatinine rose to 3.4 mg/dl; hence, amphotericin was substituted with oral fluconazole. Tacrolimus dose was titrated as per the trough levels (8 ng/ml) to 3.5 mg per day. Serum creatinine levels reached a nadir of 1.5 mg/dl by 20th day.

One month posttransplant, the patient was admitted with acute graft dysfunction (serum creatinine 2.3 mg/dl). She was euvolemic and had hyponatremia (121 mEq/l) and hypokalemia (3.1 mEq/L) with normal anionic gap metabolic acidosis (NAGMA). Thyroid function tests were normal, and urinary spot sodium was 67 mmol/l, suggestive of renal losses. Tacrolimus level was 3.85 ng/ml, and Doppler study showed normal vascularity. Graft biopsy showed features of acute tubular necrosis (ATN) without any chronicity changes or rejection. She responded to IV fluids (3 l) and oral potassium supplements. Serum creatinine progressively reduced to 1.48 mg/dl. At that point, hyponatremia was attributed to recovering ATN; hence, patient was continued on oral salt supplements. Attempts to reduce oral salt were made in outpatient visits; however, she used to develop hyponatremia, and therefore, oral salt supplement was continued.

She was admitted 18 months later, again with acute graft dysfunction. Serum creatinine had risen from 1.3 to 2.8 mg/dl, with no history of recent change in medication or noncompliance. She had hyponatremia (126 mEq/l),

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hypokalemia (3.3 mEq/l), and NAGMA (pH 7.35, HCO_3 19 mEq/l). Her tacrolimus level was 8.1 ng/ml. There were no obvious precipitating factors for hyponatremia. Hyponatremia was corrected with IV normal saline, and tacrolimus level was optimised to 5.6 ng/ml with dose titration to 3 mg per day. Hyponatremia improved; however, graft dysfunction persisted (serum creatinine 2 mg/dl). Hence, graft biopsy was performed again, which showed features of focal wrinkling of glomerular basement membrane, indicating chronic ischemia and moderate interstitial fibrosis with tubular atrophy involving 25%–30% of the cortical area. These changes, without any episode of acute rejection, were suggestive of chronic calcineurin inhibitor toxicity. Patient was not willing to convert to rapamycin hence tacrolimus was converted to prolonged release formulation 2.5 mg once a day (OD). Serum creatinine progressively reduced to 1.5 mg/dl. Her tacrolimus level was now 3.52 ng/ml.

After 2 weeks, oral sodium was stopped for assessing 24-h urinary sodium excretion. Within 12 h of discontinuing salt supplements, she developed fatigue and had an episode of generalized seizure. Lab parameters showed severe hyponatremia (113 mEq/l). Hyponatremia was corrected with 3% saline, following which her sensorium improved with no recurrence of convulsions. The 6 h of urine collected showed 125 mEq of sodium in it, confirming persistent salt-losing nephropathy. Oral salt supplementation 8 g/day was continued, and fludrocortisone 100 µg/day was added. She has remained stable thereafter, without graft dysfunction or hyponatremia episodes. Her oral salt requirement was reduced in follow-up outpatient department (OPD) visits with normalization of potassium levels.

Discussion

Chronic asymptomatic hyponatremia has been observed in 4%–9% of renal transplant recipients, but.[1,2] severe symptomatic hyponatremia due to salt wasting is rare.

Calcineurin inhibitor–related hyponatremia is uncommonly reported. It is suggested that cyclosporine reduces proximal tubular sodium reabsorption by decreasing sodium–hydrogen exchanger activity, while tacrolimus has a more profound effect on distal tubular function, where it upregulates the Na(+)/K(+)/2Cl(−) cotransporter and downregulates mineralocorticoid receptor expression in the distal tubule. This is thought to be responsible for developing aldosterone resistance causing salt-losing nephropathy.[3]

In our case, initially, hyponatremia was attributed to recovering ATN. However, hyponatremia persisted for 18 months in the context of elevated tacrolimus levels and graft biopsy showing Calcineurin inhibitors (CNI) toxicity, suggesting that hyponatremia was likely related to tacrolimus.

Higgins *et al*.[4] described that severe hyponatremia (<120 mEq/L) was more commonly observed with tacrolimus compared to cyclosporine; however, their patients were largely asymptomatic. Additionally, no patient had hyponatremia severe enough to cause seizures. In their study, they noted that serum potassium levels were higher in tacrolimus-treated patients. Our case had associated mild hypokalemia and NAGMA, suggesting a coexistent distal renal tubular acidosis.

Different strategies have been adopted by physicians to manage chronic hyponatremia in the posttransplant scenario. Fludrocortisone acts by overcoming aldosterone resistance. Higgins *et al*.[4] found that fludrocortisone treatment was well tolerated and not associated with fluid overload or severe hypertension. Bagchi *et al*.[5] reported a case of hyponatremia 2 weeks after transplant, which was managed with sodium bicarbonate and fludrocortisone. Sayin[6] managed a patient of tacrolimus-induced hyponatremia in a living donor kidney recipient by conversion to everolimus. However, Çağlayan *et al*.[7] showed no improvement in hyponatremia after tacrolimus conversion to everolimus and managed their patient successfully with fludrocortisone.

There are case reports of tacrolimus-induced hyponatremia being manged by conversion to cyclosporine with variable success in other solid organ transplants. Azuma *et al*.[8] reported a case of hyponatremia in a bone marrow transplant recipient receiving tacrolimus for acute graft versus host disease (GVHD). Tacrolimus was stopped, and serum sodium concentration normalized in the next 7 days. Cyclosporine used in this patient for acute GVHD did not result in recurrence of hyponatremia, suggesting that it is not a class effect. Banks *et al*.[9] reported five patients of hyponatremia among lung transplant recipients. Hyponatremia persisted in these patients despite fludrocortisone therapy. Hyponatremia resolved in three patients and significantly improved in two patients after they were switched from a tacrolimus-based to cyclosporine-based immunosuppressive regimen.

In our case, even after reduction of tacrolimus dose and optimizing tacrolimus levels, persistent salt losing resulted in severe symptomatic hyponatremia. This suggests tubular dysfunction persists despite normalization of tacrolimus levels. As in the above case reports, our patient also responded to fludrocortisone and salt supplementation.

Conclusion

We would like to highlight this uncommon side effect of tacrolimus that resulted in salt-losing nephropathy and hyponatremia-related seizures. In posttransplant patients, hyponatremia with no clear antecedent cause should raise the possibility of tacrolimus as the putative agent.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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