THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2017.75436
Med Bull Sisli Etfal Hosp 2018;52(4):310–312

Case Report

Aldosterone Resistance Due to Tacrolimus: A Case Report

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Abstract

Although more common with tacrolimus, it is known that calcineurin inhibitors may induce the development of electrolyte disorders such as hyponatremia and hyperkalemia by causing a hyporeninemic hypoaldosteronism-like syndrome. We present a 32-year-old female renal transplant patient who admitted to clinic with hyponatremia and hyperkalemia. Normal anion gap metabolic acidosis and renal tubular dysfunction were detected and after other reasons were excluded, it was considered as electrolyte disorder due to tacrolimus. No response was detected after tacrolimus conversion to everolimus and considering tubular dysfunction due to aldosterone resistance, we initiated fludrocortisone therapy and electrolyte disorders rapidly improved. Fludrocortisone therapy should be considered when hyponatremia and/or hyperkalemia due to tacrolimus are detected in renal transplant patients.

Keywords: Hyponatremia; renal transplantation; tacrolimus.

Please cite this article as "Bayraktar Çağlayan F, Koç Y, Baştürk T, Hasbal B, Sakacı T, Ahbap E, et al. Aldosterone Resistance Due to Tacrolimus: A Case Report. Med Bull Sisli Etfal Hosp 2018;52(4):310–312".

Nowadays, calcineurin inhibitors are indispensable treatment for patients after solid organ transplantation. Although it is more frequently seen with tacrolimus, it has long been known that inhibitors of the calcineurin inhibitors can lead to electrolyte disturbances such as hyponatremia and hyperkalemia.[1] With these drugs, it has been demonstrated that an entity resembling a hyporeninemic hypoaldosteronism syndrome coursing with a decrease in the aldosterone release and mineralocorticoid (MC) receptor expression may develop.[2] In our article, a case of tacrolimus-induced aldosterone resistance that responded to MC replacement but could not be treated with conversion to an mTOR inhibitor everolimus which belongs to another immunosuppressive drug group is presented.

Case Report

A 32-year-old female patient who had been followed up with sessions of peritoneal dialysis performed due to end-stage renal disease developed after amyloidosis due to familial Mediterranean fever and had a cadaveric renal transplantation in May 2016 applied to the transplantation polyclinic with complaints of nausea and fatigue on the 149th day after transplantation. Her biochemical test results were as follows: Creatinine 1 mg/dL, urea 34 mg/dL, sodium 122 mmol/L, and potassium 5.5 mmol/L. Other laboratory test results are given in Table 1. Her treatment protocol consisted of tacrolimus (6 mg/d), mycophenolate mofetil (2 g/d), and prednisolone (5 mg/d) as immunosuppressive drugs, metoprolol (100 mg/d) and doxazosin mesylate (8 mg/d) for the treatment of hypertension, trimethoprim-sulfamethoxazole for prophylaxis, magnesium preparation for hypomagnesemia, and calcium and Vitamin D preparations for osteopenia. To exclude any treatment with pseudohyponatremia agents, her current treatment and tests were analyzed. He had not recently received diuretic therapy and intravenous fluid replacement. His blood glucose

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Submitted Date: June 30, 2017 **Accepted Date:** September 03, 2017 **Available Online Date:** March 21, 2018

Table 1. Laboratory data of the patient

Urea (mg/dl)	34	Triglyceride (mg/dl)	170
Creatinine (mg/dl)	1	Total cholesterol (mg/dl)	206
Uric acid (mg/dl)	4.1	Albumin (g/dl)	3.9
Glucose (mg/dl)	76	Total protein (g/dl)	6.3
Sodium (mmol/l)	122	CK (U/L)	21
Potassium (mmol/l)	5.5	LDH (U/L)	221
Chloride (mmol/l)	92	WBC (10^3/μL)	9860
Calcium (mg/dl)	9.28	Hb (g/dL)	11.6
Phosphorus (mg/dl)	3.4	Hct %	35.1
Magnesium (mg/dl)	1.54	MCV (fL)	74.2
ALT (U/L)	22	Platelet (10^3/μL)	317000
AST (U/L)	22	24-h urinary Na (mosm/L)	340
GGT (U/L)	77	TSH (μIU/ml)	2.8
ALP (U/L)	109	Aldosterone (ng/dL) (while seated)	28

CK: Creatinine kinase; LDH: Lactate dehidrogenase; WBC: White blood cell; MCV: Mean corpuscular volume; TSH: Thyroid stimulating hormone; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma glutamyl transferase; ALP: Alkaline phosphatase.

levels were within normal limits. Albumin and triglyceride values were normal. The level of tacrolimus was within normal limits (7 ng/mL), and no pathology was observed in thyroid and liver tests. Clinically, signs of hypovolemia were present, and 24-h urine output was 3.5–4 l/day. Serum osmolarity was 260 mosm/L, and 24-h urine sodium excretion was 340 mosm, while urine output was 3.8 lt, so the test results were compatible with salt-losing nephropathies. In the blood gas - anion deficit was 10 mmol/L and urinary anion deficit was calculated as 7 mmol/L. The results were consistent with normal anion gap metabolic acidosis and renal tubular dysfunction.

The level of aldosterone (28 ng/dL when sitting) was found to be normal, and during her post-operative follow-up, hyponatremia was not observed, and the serum sodium value, including post-operative period, was over 130 mmol/L. Initially, she received 0.9% NaCl as an intravenous infusion. Parenteral fluid therapy was terminated when serum sodium level reached normal limits within 48 h. Sodium level in 24-h urine was 354 mosm/L and serum osmolarity was 284 mosm/L. During the follow-up, the sodium level gradually decreased to 120 mmol /L within 4 days. Then, tacrolimus-induced nephropathy was thought, and we switched to treatment with everolimus. During the maintenance treatment with everolimus, the patient's clinical symptoms (malaise and nausea) and serum sodium levels did not improve, so fludrocortisone treatment at daily doses of 0.1 mg was initiated. At the 48th h of the treatment, serum sodium level increased to 140 mmol/L and K+ level regressed to 3.8 mmol/L. In 24-h, urine Na decreased to 125 mmol/L/day. The patient tolerated fludrocortisone treatment (hypertension, gastric irritation, etc., were not seen), its dose was reduced to 0.05 mg/day after observation of minimal peripheral edema at the end of the 1st week. The patient whose peripheral edema regressed and blood pressure dropped within normal limits was discharged with fludrocortisone treatment. Serum Na level was found to be 138 mmol/L and K level 4.6 mmol/L at 9 months of her post-operative follow-up. She is still under our routine and regular surveillance.

Discussion

Hyponatremia after transplantation may develop for many reasons including renal tubular sodium loss relative hypervolemia (dilutional hyponatremia), post-operative early-onset polyuria all due to inhibitory effect of calcineurin, and replacement of urinary loss with hypotonic fluids.[3]

These etiological factors were excluded due to the absence of polyuria, hypervolemia, and history of parenteral fluid therapy. Hyperglycemia, hypothyroidism, diuretic, or any drug use that may cause hyponatremia in the normal patient population were not present in our patient. Clinical signs of volume depletion and increased Na level in 24-h urine in the patient's clinic suggested the presence of salt-losing nephropathy.

The first studies on various potential effects of calcineurin inhibitors given after renal transplantation on ion exchange, for example, hyperkalemia and salt-losing nephropathy by affecting Na/K-ATPase and Na-K-2Cl cotransporters were performed in 90 s.[4, 5] In the year 2002, an in vitro study showed that these drugs caused aldosterone resistance by inhibiting the transcriptional activity of human MK receptor more frequently with tacrolimus.[6] In another study published as an extension to this study, it was reported that

hyponatremia and hyperkalemia after immunosuppressive treatment were related to aldosterone resistance with an incidence rate as high as 75%.[7]

In this study conducted in patients with renal transplantation, it was shown that MC receptors in lymphocytes of patients with cyclosporine was decreased significantly compared to the normal healthy population and the reason why findings of hypoaldosteronism were observed in these patients while maintaining aldosterone level was explained.[7] In our patient, hyperkalemia accompanied by severe hyponatremia despite metabolic acidosis with normal anion gap was explained with aldosterone resistance.

In another study conducted with 125 renal transplant patients, hyponatremia and hyperkalemia had been more frequently encountered in patients using tacrolimus than in those on cyclosporine treatment. Similar to our study, nine patients with hyponatremia had been treated with fludrocortisone which was tolerated well with resultant normalization of serum sodium levels. In their study, hyponatremia developed 14–79 days after transplantation, while in our case, it developed 149 days after transplantation, similar to a case report published in 2015.[8] In all of the similar studies, tacrolimus levels were found to be normal in patients with hyponatremia as in our case. In another recent study, although serum sodium levels improved within 48 h as a result of conversion from tacrolimus to everolimus,[7] in our case, hyponatremia did not improve despite a 4-week follow-up period and the need for replacement with 0.9% NaCl solution continued. After starting fludrocortisone, serum sodium level returned to normal after 48 h and no subsequent hyponatremia was observed. In addition, some studies have shown that fludrocortisone treatment is beneficial in renal transplant patients with calcineurin nephrotoxicity.[1, 9]

Although calcineurin inhibitors may produce renal toxicity, they are the cornerstone of treatment in the renal transplantation population. Although a case report regarding a patient with tacrolimus-associated hyponatremia.[8] That responded to conversion to everolimus, it may not be appropriate to remove tacrolimus from the treatment protocol, particularly in the immunologically high-risk patient group. Fludrocortisone treatment can be preferred for this purpose due to its easy availability, rapid dose titration, and low side effect profile. However, despite the cessation of tacrolimus in our patient, hyponatremia could not improve, suggesting that this effect may be irreversible or may be accompanied by different mechanisms. There is a continuing need for further studies in this area.

Conclusion

In patients with renal transplantation, renal tubular dysfunction may occur despite normal tacrolimus levels and this condition should be kept in mind when hyponatremia develops. Fludrocortisone is effective and useful in the treatment of aldosterone-resistant salt-losing nephropathy. When hyponatremia is detected in the renal transplant patient, and tacrolimus-induced hyponatremia is considered after exclusion of other etiologies, fludrocortisone should be kept in mind as an effective treatment alternative.

Disclosures

Informed consent: Written informed consent was obtained from the patient for the publication of the case report.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship contributions: Concept – Y.K.; Design – F.B.Ç.; Supervision – Y.K., T.B.; Materials – F.B.Ç., P.N.; Data collection &/or processing – F.B.Ç., B.H.; Literature search – P.N., M.İ.; Writing –F.B.Ç.; Critical review – T.S., E.A., A.Ü.

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