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# Masked Arginine Vasopressin Deficiency in a Kidney Transplant Recipient With Posttransplant Lymphoproliferative Disorder



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## INTRODUCTION

Posttransplant lymphoproliferative disorder (PTLD) is the second most common cancer to occur after organ transplantation, accounting for approximately 20% of all cancers post kidney transplant.[1] PTLD is most common in gastrointestinal tract (20%–30%), followed by central nervous system (CNS) (5%–15%), and allograft (5%).[2] In rare cases, CNS-PTLD can involve the hypothalamus and pituitary gland (<0.5%).[3] Clinical presentation of PTLD is nonspecific and variable, ranging from generalized fatigue to neurological symptoms such as ataxia and seizures.

Arginine vasopressin deficiency (AVP-D), formerly known as central diabetes insipidus, is a rare complication of CNS lymphoma. AVP-D typically presents with polyuria, polydipsia, and hypernatremia. However, these typical signs and symptoms can remain masked in patients with panhypopituitarism.

In this case report, we aim to discuss the diagnostic challenges of AVP-D in a kidney transplant recipient with CNS-PTLD and clinical management considerations with high-dose methotrexate therapy (MTX) (Table 1).

## CASE PRESENTATION

A 62-year-old male with a history of autosomal dominant polycystic kidney disease underwent a preemptive living unrelated donor kidney transplant (Epstein-Barr virus IgG: donor positive, recipient positive). He had no history of allograft rejection, and the immunosuppression regimen consisted of tacrolimus (goal trough level 6–8 ng/ml), mycophenolate mofetil 1000 mg twice daily, and prednisone 2.5 mg daily. Eight years after the transplant, the patient presented with lethargy and acute right lower quadrant abdominal pain. He was diagnosed with monomorphic PTLD consistent with stage 4 diffuse large B cell lymphoma (International Prognostic Index 4; immunohistochemistry of the tumor tissue demonstrated expression of MYC, BCL2, and BCL6, and negativity of Epstein-Barr virus-encoded small RNA) involving multiple nodal and extranodal sites, including liver, small bowel, peritoneum, lung, and left humerus. There were no metastases to the adrenal glands. Mycophenolate mofetil was discontinued. The patient received 6 cycles of chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone plus CNS prophylaxis with intrathecal MTX and cytarabine. He initially achieved complete response; however, 2 months after completing chemotherapy, the patient presented with weakness and hyponatremia (Na: 121 mEq/l, serum osmolality: 258 mOsm/kg, spot urine osmolality: 178 mOsm/kg, and urine Na: 45 mEq/l). The workup demonstrated panhypopituitarism (Table 2). Prednisone was increased from 2.5 mg to 10 mg daily without improvement of symptoms.

Several weeks later, the patient presented with persistent anorexia; diarrhea; weight loss; and neurologic deficits, including ataxia, urinary incontinence, and mild dysarthria. Magnetic resonance imaging of the brain and spine revealed masses involving the left lateral ventricle, hypothalamus, and the third ventricle, as well as leptomeningeal enhancement (Supplementary Figure S1A). Positron emission tomography scan

**Table 1.** Teaching points

1. Arginine vasopressin deficiency (AVP-D), formerly known as central diabetes insipidus, can present with atypical signs and symptoms. Comprehensive assessment of the pituitary-adrenal axis is crucial.
2. In the presence of panhypopituitarism, AVP-D can be unmasked by high-dose glucocorticoid and is characterized by sudden onset polyuria, polydipsia, and mild hypernatremia.
3. Temporary interruption of vasopressin therapy should be considered in patients with CNS lymphoma with AVP-D, particularly during high volume fluid administration (e.g., sodium bicarbonate infusion after high-dose methotrexate).

CNS, central nervous system.

confirmed FDG-avid lesions in the posterior thigh, tongue base, and suprasellar involvement, but without any evidence of adrenal gland involvement. Cerebral spinal fluid cytology confirmed the presence of malignant B cells, and biopsy of left sphenoid mass confirmed EBV-negative diffuse large B cell lymphoma (Supplementary Figure S2), indicating relapsed PTLD-diffuse large B cell lymphoma with CNS involvement. He began treatment with high-dose MTX and dexamethasone (40 mg daily). Tacrolimus was discontinued and the patient remained only on prednisone 10 mg daily for immunosuppression. Levothyroxine 88 mcg daily was started for hypothyroidism. Shortly after a dose of dexamethasone, the patient reported insurmountable thirst with increased urinary output, averaging 4 to 10 l/d. Laboratory results showed: Na 131 mmol/l, Cr 1.0 mg/dl, spot urine osmolality 126 mOsm/kg, and urine sodium 50 mEq/l. The vasopressin test (Supplementary Table S1) yielded more than a 2-fold increase in the urine osmolality and copeptin level $<$ 2.8 pmol/l with serum Na 150 mmol/l, confirming the diagnosis of AVP-D. The patient was started on oral desmopressin 0.05 mg daily, which was titrated up to maintain urine output to approximately 2 l/d. Subsequently, the patient underwent 3 more cycles of high-dose MTX therapies. Due to concomitant desmopressin therapy and urine alkalinization protocol with sodium bicarbonate infusion (150 ml/h) during high-dose MTX, the patient developed acute hyponatremia (nadir 127 mEq/l). Ultimately, desmopressin was held at the start of each cycle of high-dose MTX therapy to maintain eunatremia. Although he initially achieved partial response (Supplementary Figure S1B), PTLD progressed after several lines of targeted therapies and autologous stem cell transplant, and the patient eventually chose palliative care.

**Table 2.** Endocrine labs highlight hypopituitarism and central diabetes insipidus diagnosis

| Laboratory findings | Values | Normal range |
|---|---|---|
| ACTH | $<$ 5 pg/ml | 6–50 pg/ml |
| Morning cortisol | $<$ 1.0 ug/dl | 5–25 mcg/dl |
| FSH | 1.5 IU/l | 1.5–12.4 IU/l |
| LH | $<$ 0.1 IU/l | 1.8–8.6 IU/l |
| Prolactin | 48 ng/ml | 4–15.2 ng/ml |
| TSH | 0.03 mIU/ml | 0.5–4.59 mIU/l |
| T4 | 4.5 ug/gl | 5–12 ug/dl |
| Free T4 | 0.8 ng/dl | 0.8–1.8 ng/dl |
| Total testosterone | $<$ 1 ng/dl | 250–1100 ng/dl |
| Copeptin | $<$ 2.8 pmol/l | 2.8–11.3 pmol/l |

ACTH, adrenocorticotropic hormone; FSH, follicle stimulating hormone; LH, luteinizing hormone; TSH, thyroid stimulating hormone; T4, thyroxine.

## DISCUSSION

This case illustrates the diagnostic and clinical management challenges of AVP-D associated with CNS-PTLD. AVP-D is characterized by the inability to maximally concentrate the urine and typically presents with polyuria, polydipsia, and hypernatremia. With concomitant panhypopituitarism, patients can present with hyponatremia, and polyuria or polydipsia can be masked. In these cases, the typical signs and symptoms of AVP-D may only become evident (i.e., unmasked) after glucocorticoid therapy.

The exact mechanism of how glucocorticoid administration unmasks AVP-D is not entirely clear, but there are 4 proposed mechanisms. First, glucocorticoid inhibits filamentous actin polymerization and thereby inhibits intracellular vesicular transport of aquaporin 2 to the apical surface of the collecting duct cells, subsequently decreasing free water reabsorption.[4] Second, glucocorticoid inhibits AVP signaling at or post vasopressin V2 receptor level leading to downregulation of apical expression of aquaporin 2 in the collecting duct.[5] Third, glucocorticoid transcriptionally suppresses expression of AVP and downregulates the secretion of AVP from hypothalamus, and thereby further aggravates excessive free water loss.[6,7] Lastly, glucocorticoid administration increases circulatory volume and cardiac output, and may inhibit nonosmotic stimulation of AVP secretion.[8]

Desmopressin is the standard of treatment for AVP-D and close monitoring of sodium concentrations is needed, especially with isotonic fluid administration. In addition, high-dose MTX therapy is the first-line therapy for CNS lymphoma, which requires high volumes of sodium bicarbonate infusion for urine alkalinization to enhance MTX clearance. The combination of desmopressin therapy and isotonic fluid administration can lead to severe hyponatremia. In the setting of vasopressin therapy, clinicians must be aware of the risk of hyponatremia and carefully adjust or hold vasopressin temporarily during high-dose MTX therapy. Conversely, the management of hypernatremia is equally critical, especially when acquired in the hospital due to the associated increased mortality.[9] This is largely accomplished by allowing the patient access to

free water, addressing volume status, and closely monitoring sodium levels.

In conclusion, AVP-D can be masked when a patient has concomitant panhypopituitarism due to CNS-PTLD and lead to overt symptoms once glucocorticoid supplementation is initiated. This presentation may be underrecognized in kidney transplant patients and thus vigilance of electrolytes and volume status is needed.

## DISCLOSURE

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## PATIENT CONSENT

The authors have obtained consent from the family of the deceased patient discussed in the report.

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## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Figure S1.** Magnetic resonance brain images before and after therapy.

**Figure S2.** Histopathology of tumor biopsy.

**Table S1.** Serum and urine lab results preceding and following diagnosis of AVP-D.

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