Tolvaptan for SIADH in Myelodysplastic Syndrome with Blast Crisis

Padmavathi Mali, MD; Sudheer R. Muduganti, MD; Rahaman Mujibur, MD; Narayana Murali, MD

ABSTRACT

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a common cause of hyponatremia in cancer patients. It is most frequently reported in association with small-cell lung cancer, but has been reported in other cancers as well. Here we report the case of a patient with myelodysplastic syndrome and blast crisis who developed concurrent hyponatremia. The patient failed to respond to fluid restriction and administration of hypertonic saline. She was treated with tolvaptan, a vasopressin antagonist licensed for the treatment of adult patients with hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion. We conclude that in myelodysplastic syndrome patients with blast crisis, inappropriate antidiuretic hormone secretion should be considered as a cause of hyponatremia and be treated with tolvaptan.

INTRODUCTION

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) causes dilutional hyponatremia by increasing secretion of antidiuretic hormone (ADH) and water reabsorption in collecting ducts and is a common cause of hyponatremia in cancer patients.[1] SIADH has been reported most commonly in small-cell lung cancer, but has been described in other cancers as well.[1] In the literature, there is only 1 case report of SIADH in a patient with acute myeloid leukemia (AML) with multilineage dysplasia who developed hyponatremia and showed symptoms of SIADH through a mechanism similar to tumor lysis.[2] We report a case of hyponatremia from SIADH in a patient with myelodysplasia with blast transformation who showed a positive response to tolvaptan, a vasopressin antagonist licensed for the treatment of adult patients with hyponatremia secondary to SIADH.[3]

• • •

Author Affiliations: Department of Internal Medicine, Marshfield Clinic, Marshfield, Wis (Mali, Muduganti, Mujibur); Department of Nephrology, Marshfield Clinic, Marshfield, Wis (Murali).

Corresponding Author: Padmavathi Mali, MD, Department of Internal Medicine, Marshfield Clinic, 1000 N Oak Ave, Marshfield, WI 54449; phone 715.387.5537; e-mail mali.padmavathi@marshfieldclinic.org.

CASE PRESENTATION

A 66-year-old woman was admitted to the hospital with chest pain. She had a diagnosis of myelodysplastic syndrome (MDS) and her most recent bone marrow aspirate showed hypercellular marrow with severe reticulin fibrosis and an increase in myeloblasts, suggestive of evolving MDS classified as refractory anemia with excess blasts-2 (RAEB-2). She received 4 cycles of azacitidine as an outpatient in anticipation of getting bone marrow aspiration before the fifth cycle. One week before hospital admission, her sodium level was 135-137 mmol/L (normal 133-144 mmol/L).

The patient was admitted for chest pain described as substernal, pressure-like, and nonpositional. Her physical examination was unremarkable, and her laboratory results showed a white blood cell count (WBC) of 13,700/μL (normal 4,100–10,900/μL) with 6% blast cells, 46% neutrophils, 26% lymphocytes, 11% monocytes, 1% basophils, and 10% myelocytes and metamyelocytes. Additional laboratory results showed normal hemoglobin (11.6 g/dL), platelets (213,000/ml), and creatinine (0.5 mg/dL) with low levels of sodium (133 mmol/L, normal 133-144 mmol/L) and urea nitrogen (5 mg/dL, normal 6–24 mg/dL), and an elevated D-dimer of 2.5 μg/mL (normal 0.1–0.67 μg/mL). A subsequent computed tomography (CT) scan of the chest was negative for pulmonary embolism, but the patient's bones were diffusely sclerotic due to underlying MDS, and this was determined to be the cause of her chest pain. She was started on narcotic analgesics for pain and continued on her home medications, including fluoxetine.

The next day, the patient's sodium level had dropped to 127 mmol/L, reaching 120 mmol/L in the next 2 days. Although the patient was euvolemic on clinical examination, her laboratory results showed low serum osmolality at 253 mOsm/kg (normal 282-305 mOsm/kg), urine sodium at 45 mmol/L, serum uric acid at 1.8 mg/dL (normal 2.3-6.4 mg/dL), and urine osmolal-

ity at 566 mOsm/kd (normal 500-800 mOsm/kg). Urinalysis revealed a specific gravity of 1.023 (normal 1.002-1.030) and was negative for protein and ketones. She had normal renal function and no evidence of hypothyroidism or adrenal insufficiency, but serum ADH, which was measured to confirm the SIADH diagnosis, was elevated at 3.5 pg/mL. These findings are consistent with the mild volume expansion expected in SIADH.

Table. Change in Serum Sodium Level, Urine Osmolality, and Urine Sodium Over Time

Day	Serum Sodium (mmol/L)	Intervention	Urine Osmolality (mOsm/kg)	Urine Sodium (mmol/L)
-7	137			
0	133	Admission		
2	127			
3	125		566	< 5
4	120		253	
5	117	Intensive Care Unit and 3% saline		
6	122	Fluoxetine discontinued, fluid restriction		
7	122	Fluid restriction		
8	122	Fluid restriction, tolvaptan (15 mg)	691	
9	124	Fluid restriction, tolvaptan (15 mg)	425	
10	129	Fluid restriction, tolvaptan (15 mg)		
11	133			45
25	133			

On the fourth day after admission, the patient's total WBC increased to 23,500/μL with 38% blasts. Approximately 40% of cells were circulating myeloblasts indicating evolution to (AML). Circulating myeloblasts were found to express CD45, CD34, CD117, CD33, CD13, HLA-DR, CD11b, and CD11c with CD64 expression at moderate intensity and no CD14 expression, suggesting no evidence of monocytic differentiation. This immunophenotype was quite different from the myeloblasts in the bone marrow, which were CD117-positive and CD34-negative.

By day 5, the patient's sodium continued to drop to 117 mmol/L, and she developed signs of altered mental status with confusion. She was placed in the intensive care unit overnight and started on a 3% saline infusion. With the diagnosis of SIADH as the cause of hyponatremia, fluoxetine was discontinued, and she was placed on fluid restriction. Subsequently, her sodium level increased to 122 mmol/L, and her mental status improved. She was continued on fluid restriction, and her sodium level remained at 122 mmol/L for the next 3 days. Urinalysis on fluid restriction showed an increase in specific gravity from 1.023 to 1.036, and urine osmolality increased from 566 to 691 mOsm/kg. On day 7, she was started on hydroxyurea 500 mg 3 times daily when her WBC increased to 38,000/μL. She also received packed red cell transfusions for worsening anemia and had worsening thrombocytopenia for which she did not require platelet transfusions.

On day 8, the patient's sodium level was 122 mmol/L, and she was started on tolvaptan 15 mg per day, which was continued for the next 3 days. Her sodium level increased progressively to 133 mmol/L (Table). Urine output on tolvaptan was 1 liter on day 1, 500 ml on day 2, and 1100 ml on day 3. She was in negative balance all 3 days.

Retrospectively, the bone marrow biopsy was sent for immunohistochemical analysis, and blast cells were negative for ADH.

DISCUSSION

Hyponatremia from SIADH is a common electrolyte abnormality seen in patients most often due to a small cell carcinoma of the lung and is rarely seen with other lung tumors.[4] Less common causes of malignancy-associated SIADH include head and neck cancers, olfactory neuroblastoma (esthesioneuroblastoma), and extrapulmonary small cell carcinomas. In the literature, there is one other case report of SIADH in a patient with AML with multilineage dysplasia who developed hyponatremia and showed symptoms of SIADH through a mechanism similar to tumor lysis.[2] This is the first case of hyponatremia from SIADH in a patient with myelodysplasia with blast transformation.

Evidence suggests that hyponatremia in cancer patients may be a negative prognostic factor,[1] making recognition and appropriate treatment particularly important. In the patient described here, the diagnosis of SIADH was based on clinical status and laboratory values after ruling out thyroid and adrenal insufficiency. It is also important to exclude the potential influence of drugs on hyponatremia. In the patient presented here, we began treatment of hyponatremia by discontinuing fluoxetine with fluid restriction. Fluoxetine has relatively slow elimination with a half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration.[5] The patient had been on fluoxetine for several months before admission with no history of hyponatremia. Sudden development of hyponatremia concurrent with development of AML prompted us to look for other causes, including blast-induced hyponatremia.

In patients with cancer, hyponatremia is often the result of SIADH and is thought to be caused by the ectopic production of arginine vasopressin (AVP) by tumor tissues or the effects of anticancer and palliative medications on AVP production or action.[6] In a single case report in the literature, blast cells were reported to stain positive for ADH in a patient with AML and SIADH.[2] In the present case, bone marrow was negative for ADH by immunohistochemical staining, but the interpretation and pathology results may be of limited value due to decalcification of the sample. Therefore, we are unable to rule out the tumor tissue as a source of ADH.

In the treatment of hyponatremia, hypertonic saline is indi-

cated for acute, symptomatic cases,[7] whereas fluid restriction is recommended to achieve a slower rate of correction for chronic asymptomatic hyponatremia. However, such measures may be insufficient to correct electrolyte imbalance in some. As illustrated in the case presented here, pharmacological therapy with tolvaptan may be necessary when fluid restriction is insufficient. Tolvaptan blocks the effects of AVP in the renal collecting duct to promote aquaresis, leading to a controlled increase in serum sodium levels by inducing free water excretion without increasing sodium excretion.[8] The effects of tolvaptan therapy in our patient were evident as serum sodium levels increased and urine osmolality decreased. Tolvaptan administration achieved a controlled increase in sodium levels to within the normal range, which fluid restriction failed to do.

Tolvaptan is available as 15 mg or 30 mg tablets. Treatment should be initiated at a dose of 15 mg once daily and titrated to a maximum dose of 60 mg once daily. Treatment is needed until the underlying cause of hyponatremia is corrected. Regular monitoring of serum sodium concentrations and volume status are necessary if tolvaptan is used in the outpatient setting. Tolvaptan therapy should be undertaken with caution due to the risk for adverse effects and potential drug interactions. Adverse effects reported most frequently include thirst and dry mouth, in addition to rarer reports of hypernatremia, pollakiuria, and polyuria.[9] Tolvaptan is metabolized by the cytochrome P450 isoenzyme CYP3A4, which is involved in the metabolism of a large number of common drugs, resulting in a high risk of pharmacokinetic interactions.[10]

CONCLUSION

The etiology of hyponatremia is diverse, and systemic evaluation is important for defining the cause and formulating a treatment plan. SIADH should be considered as a potential cause of hyponatremia in MDS patients with blast crisis. The vasopressin antagonist tolvaptan can be used to correct the hyponatremia if conservative treatments fail.

Acknowledgements: The authors thank the Marshfield Clinic Research Foundation Office of Scientific Writing and Publication for assistance in preparing this manuscript.

Funding/Support: None declared.

Financial Disclosures: None declared.

REFERENCES

1. Castillo JJ, Vincent M, Justice E. Diagnosis and management of hyponatremia in cancer patients. *Oncologist.* 2012;17:756-765.

2. Nakayama S, Yokote T, Kobayashi K, et al. Syndrome of inappropriate antidiuretic hormone secretion associated with acute myeloid leukemia with multilineage dysplasia. *Endocrine.* 2009;35:290-292.

3. Ghali JK, Hamad B, Yasothan U, Kirkpatrick P. Tolvaptan. *Nat Rev Drug Discov.* 2009;8:611-612.

4. Johnson BE, Chute JP, Rushin J, et al. A prospective study of patients with lung cancer and hyponatremia of malignancy. *Am J Respir Crit Care Med.* 1997;156:1669-1678.

5. Prozac, Clinical Pharmacology. RxList: The Internet Drug Index. Available at: www.rxlist.com/prozac-drug/clinical-pharmacology.htm. Accessed March 3, 2015.

6. Raftopoulos H. Diagnosis and management of hyponatremia in cancer patients. *Support Care Cancer.* 2007;15:1341-1347.

7. Sterns RH, Nigwekar SU, Hix JK. The treatment of hyponatremia. *Semin Nephrol.* 2009;29:282-299.

8. Gheorghiade M, Gottlieb SS, Udelson JE, et al. Vasopressin v(2) receptor blockade with tolvaptan versus fluid restriction in the treatment of hyponatremia. *Am J Cardiol.* 2006;97:1064-1067.

9. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med.* 2006;355:2099-2112.

10. Shoaf SE, Bricmont P, Mallikaarjun S. Effects of CYP3A4 inhibition and induction on the pharmacokinetics and pharmacodynamics of tolvaptan, a non-peptide AVP antagonist in healthy subjects. *Br J Clin Pharmacol*. 2012;73:579-587.

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

Visit www.wmjonline.org to learn more.