CASE REPORT

A case of SIADH escape to tolvaptan from small cell lung cancer

Sunny Mandal[1],Mwangi Kamau[2], Lakshmi Kannan[3]

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ABSTRACT

BACKGROUND: Syndrome of inappropriate antidiuresis is characterized by euvolemic hyponatremia due to inappropriate secretion or elevation of antidiuretic hormone or arginine vasopressin. Patients with small cell lung cancer are especially prone for this complication and multiple randomized control trials have shown an improvement in sodium with tolvaptan.

CASE: We report a 61-year-old-male patient with small cell lung cancer who presented with to the hospital multiple times with acute on chronic symptomatic hyponatremia. The patient showed a good response to tolvaptan but subsequently developed resistance as a result of progression of lung cancer with metastasis to liver.

CONCLUSION: In cases of paraneoplastic effects of lung cancer, hyponatremia is an important manifestation from syndrome of inappropriate antidiuresis. Hyponatremia, in these patients, is associated with significant morbidity and mortality and treatment includes surgery, chemotherapy or radiation therapy for the cancer, tolvaptan for hyponatremia and in cases of progression of cancer, addition of salt tablets or loop diuretics may be necessary.

Key Words: *SIADH; Tolvaptan; Hyponatremia; Small cell lung cancer; ADH*

INTRODUCTION

Hyponatremia is a common serum electrolyte abnormality known to be an independent predictor of morbidity and mortality in hospitalized patients. One potential cause of euvolemic hyponatremia is through the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) by way of ectopic production of Antidiuretic Hormone (ADH). This occurs in 11%-15% of cases of patients with Small Cell Lung Cancer (SCLC) [1]. The pathophysiology through which ectopic ADH is secreted in SCLC patients may vary with multiple contributing factors- direct tumor secretion, enhanced secretion of ADH due to adrenal metastases, chemotherapy, opioids, non-steroidal anti-inflammatory drugs, or from side effects of treatment such as nausea, vomiting, stress, and pain.

Tolvaptan is an orally active nonpeptide antagonist of arginine vasopressin from binding to V2 receptors of the distal nephron inducing electrolyte-free water excretion. It is a breakthrough, safe and effective therapy for promoting aquaresis and raising serum sodium levels in short- and long-term studies. We report a patient with small-cell lung cancer who was initially managed with tolvaptan but subsequently developed resistance to the aquaretic effects of the drug.

CASE PRESENTATION

A 61-year-old white male with a history of small cell lung cancer diagnosed 11 months prior to presentation and chronic hyponatremia on tolvaptan 30 mg daily presented with primary complaints of unsteady gait and weakness.

[1]*University of Pikeville-Kentucky College of Osteopathic Medicine, Pikeville, KY, USA 41501;* [2]*We Care Nephrology LLC, 100 Kings Hwy, Milford, Delaware-19963, US;* [3]*Department of Internal Medicine, Division of Nephrology, Pikeville Medical Center, Pikeville, KY, USA 41501*

Correspondence: Lakshmi Kannan,Department of Internal Medicine, Division of Nephrology, Pikeville Medical Center, Pikeville, KY, USA 41501 e-mail lakshmi.kannan@pikevillehospital.org

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Initial evaluation revealed he was afebrile with a blood pressure of 104 mm Hg/45 mm Hg and a heart rate of 86 beats per minute. Physical examination was positive for generalized weakness but otherwise unremarkable. Laboratory work-up showed serum sodium of 111 mEq/L with serum osmolality of 236 mOsm/ Kg water, urine osmolality of 589 mOsm/Kg water, and urine sodium of 62 mEq/L. The patient's baseline sodium was 122 mEq/L-125 mEq/ L. He was diagnosed with a syndrome of inappropriate antidiuresis secondary to small-cell lung cancer and was admitted to the intensive care unit (ICU) for 3% hypertonic saline. His sodium slowly improved to 120 mEq/L with a resolution of his symptoms. Tolvaptan 30 mg daily was resumed with improvement in his sodium to 124 mEq/L at the time of discharge. Reviewing his records, the patient was diagnosed with T3N3 IIIC small cell lung cancer approximately 11 months prior to this most recent hospitalization (Figure 1). He underwent two cycles of chemotherapy with cisplatin and etoposide.

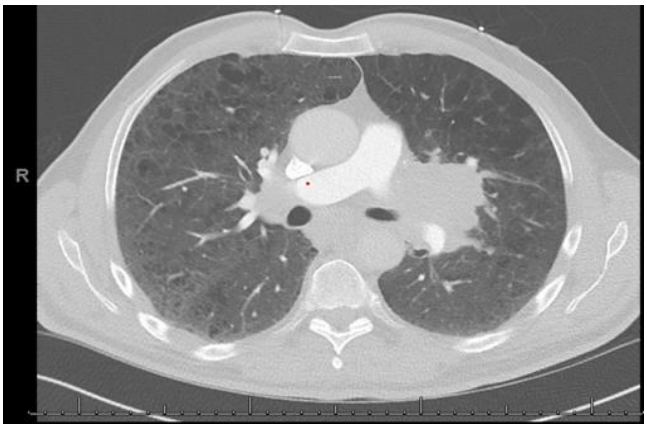

Figure 1) *Multilobulated left hilar mass measuring at least 7.0 cmx5.9 cmx6.4 cm*

Successively, he was found to have a solitary liver metastasis requiring radiation therapy. This was complicated by severe esophagitis requiring Percutaneous Endoscopy Gastrostomy (PEG) tube placement. In 3 months, the patient had three hospitalizations for acute on chronic hyponatremia. During one of his hospitalizations, the patient's tolvaptan dose was increased to 45 mg daily but was not tolerated due to side effects of extreme thirst and polyuria. In his most recent admission, a Computed Tomography (CT) of the abdomen/pelvis revealed multiple new liver metastases requiring Oncology follow-up for further chemotherapy. The timeline of events is shown in Figure 2.

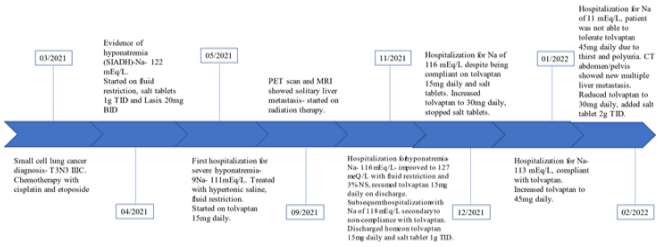

Figure 2) *Timeline of events*

DISCUSSION

Syndrome of Inappropriate Antidiuretic Hormone (SIADH) is characterized by euvolemic hypotonic hyponatremia due to inappropriate elevation of Plasma Arginine Vasopressin (pAVP) or Antidiuretic Hormone (ADH). Tolvaptan was approved for use in SIADH since May 2009. Its mode of action is through blocking the vasopressin 2 receptor leading to a reversal of hyponatremia in patients with SIADH. The hyponatremia registry enrolled hyponatremia patients from 146 US and 79 European sites. Burst et al determined of the euvolemic patients, 5028 on the registry, 21% of the cases were cancer-related with lung cancer accounting for the majority at 53.4% of cases. SIADH was the primary cause of hyponatremia in 95% of cancer-related euvolemic hyponatremia [2]. In the SALTWATER study, 52.3% of patients enrolled had a diagnosis of SIADH [3]. During the follow-up period of 701 days, serum sodium levels remained within the normal range without reported cases of de novo hyponatremia. The first two cases of resistance to tolvaptan therapy were described in 2018 on patients with small-cell lung cancer [4]. To our knowledge, this is the third report of SIADH escape to tolvaptan.

CONCLUSION

The possible cause for this resistance to the aquaretic effects of the drug is likely due to extraordinarily high ADH levels. This would overwhelm the capacity of tolvaptan to compete at the renal V2 receptors. The increased levels may represent a sign of disease progression rather than non-compliance. In these cases, successful treatment of the malignancy will eliminate or reduce the inappropriate ADH secretion. Nevertheless, pharmacological intervention is most often required, included in this arsenal is tolvaptan. But in cases of progressive cancer accounted for by new metastasis, tolvaptan may not be enough and additional therapy plans such as fluid restriction, diuretics, and salt tablets need to be considered.

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STATEMENT OF ETHICS

Our institution does not require ethical approval for reporting individual cases. This retrospective review of patient data did not require ethical approval in accordance with local or national guidelines. Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the authorship, and/or publication of this article.

AUTHOR CONTRIBUTIONS

Sunny Mandal designed the study and contributed to the case presentation and discussion. Lakshmi Kannan contributed to the

timeline of events. Mwangi Kamau contributed to the review of the manuscript.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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