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When Silence Can Be Dangerous: Recurrent Profound Hyponatremia Secondary to SIADH and the Therapeutic Role of Tolvaptan

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Abstract

Introduction: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) can cause euvolemic hyponatremia, especially in patients with head and neck malignancy and surgeries or post- thyroidectomy histories. This condition increases the therapeutic challenge and the risk of recurrent hospitalizations.

Case Presentation: A 70-year-old patient with a history of total laryngectomy secondary to laryngeal squamous cell carcinoma, partial pharyngectomy, and papillary thyroid carcinoma status post thyroidectomy, presented to the emergency department with acute chest pain, nausea, and vomiting. Cardiac markers were negative for acute coronary disease, while her serum sodium was 116 mmol/L, and a serum osmolality of 246 mOsm/kg, urine osmolality 670 mOsm/kg, urine sodium of 38 mmol/L, and serum uric acid of 2.4 mg/dL. The patient was admitted to the intensive care unit (ICU) for severe hyponatremia. She was managed with fluid restriction, oral urea, and hypertonic saline. Basic metabolic panels (BMPs) were followed up every three hours. Urine studies confirmed the diagnosis of SIADH. She received tolvaptan at 7.5 mg once, resulting in rapid and sustained correction of serum sodium to 134 mmol/L without neurologic complications. She was discharged with stable sodium levels and experienced several admissions for recurrent hyponatremia with serum sodium of 120s mmol/L, each time responding well to tolvaptan.

Discussion: This case emphasizes the clinical challenge of managing recurrent severe SIADH in patients with head and neck malignancy. It demonstrates that low-dose tolvaptan may serve as an effective therapeutic choice for refractory SIADH. However, the cost of tolvaptan could be a barrier for outpatient settings.

Keywords: ***Hospitalized patients; Syndrome of inappropriate antidiuretic hormone secretion (SIADH); Hyponatremia; Malignancy; Laryngeal squamous cell carcinoma; Small cell lung carcinoma; Partial pharyngectomy; Papillary thyroid carcinoma; Thyroidectomy; Osmolality; Tolvaptan***

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1. Introduction

Hyponatremia is one of the most common electrolyte imbalances in hospitalized patients, approximately 29.36% [1-3]. The majority of hospitalized patients were elderly (>60 years) (215/48.72%) and male (201/58.40%), commonly diagnosed with liver diseases (48/13.68%), endocrine disorders (47/13.39%), and syndrome of inappropriate antidiuretic hormone secretion (46/13.11%), multifactorial and comorbidities [3]. Hyponatremia is associated with increased mortality, length of stay, and neurologic complications [4]. In oncology populations, its prevalence is even higher, ranging from 20%-40%, depending on tumor type and stage [5].

Hyponatremia in the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a dilutional, euvolemic state caused by excess, unregulated ADH, which leads the kidneys to retain water while excreting sodium due to non-osmotic release of arginine vasopressin (AVP) or an enhanced renal response to AVP [6]. Patients with post-surgical status stemming from tumor-related paraneoplastic ADH production, baroreceptor-mediated hormone release during neck surgery, and post-thyroidectomy hormone withdrawal could cause hyponatremia and SIADH [7]. Malignancy accounts for approximately 20%-30% of SIADH cases and remains the most common paraneoplastic endocrine disorder [7,8]. Small cell lung carcinoma is classically associated with SIADH, head and neck malignancies, including laryngeal squamous cell carcinoma, and has increasingly been recognized as a trigger through ectopic ADH production, postoperative hypothalamic–pituitary axis disruption, inflammation-mediated AVP release, and chemotherapy-induction [7,9-14]. This report highlights recurrent hyponatremia secondary to malignancy-associated SIADH in a patient and discusses the pathways by which cancer induces chronic sodium dysregulation and the therapeutic role of tolvaptan.

2. Case Presentation

A 70-year-old female with a history of total laryngectomy for laryngeal squamous cell carcinoma, partial pharyngectomy, and papillary thyroid carcinoma status post thyroidectomy presented with acute chest pain, nausea, and vomiting. She denied diuretic use, heart failure symptoms, or liver disease. Initial evaluation demonstrated:

Hyponatremia Workup Labs

Test	Value	Normal Range
Serum Sodium	116 mmol/L	135-145 mmol/L
Serum Osmolality	246 mOsm/kg	275-295 mOsm/kg
Urine Osmolality	670 mOsm/kg	50-100 mOsm/kg*
Urine Sodium	38 mmol/L	<20 mmol/L (varies)**
Serum Uric Acid	2.4 mg/dL	3.5-7.2 mg/dL
TSH	1.5 mIU/L	0.4-4.0 mIU/L
Cortisol	12 µg/dL	5-25 µg/dL (AM)
Creatinine	0.9 mg/dL	**0.6-1.3 mg/dL**

Troponin was within the normal range, and the electrocardiogram (ECG) showed a normal sinus rhythm without ST-segment changes. Physical examination was unremarkable. She was admitted to the ICU for closer monitoring. She was managed with fluid restriction (1 L/day), oral urea 15 g daily, a single 100 mL bolus of 3% hypertonic saline, and BMP checks every 3 hours. Despite therapy, sodium remained <120 mmol/L. A single 7.5 mg dose of tolvaptan was administered. Within 24 hours, sodium increased to 126 mmol/L and subsequently stabilized at 134 mmol/L without osmotic demyelination or overcorrection. She was discharged with stable sodium levels. Over the following months, she experienced multiple admissions with sodium levels in the 120s mmol/L. Each episode responded rapidly to low-dose tolvaptan.

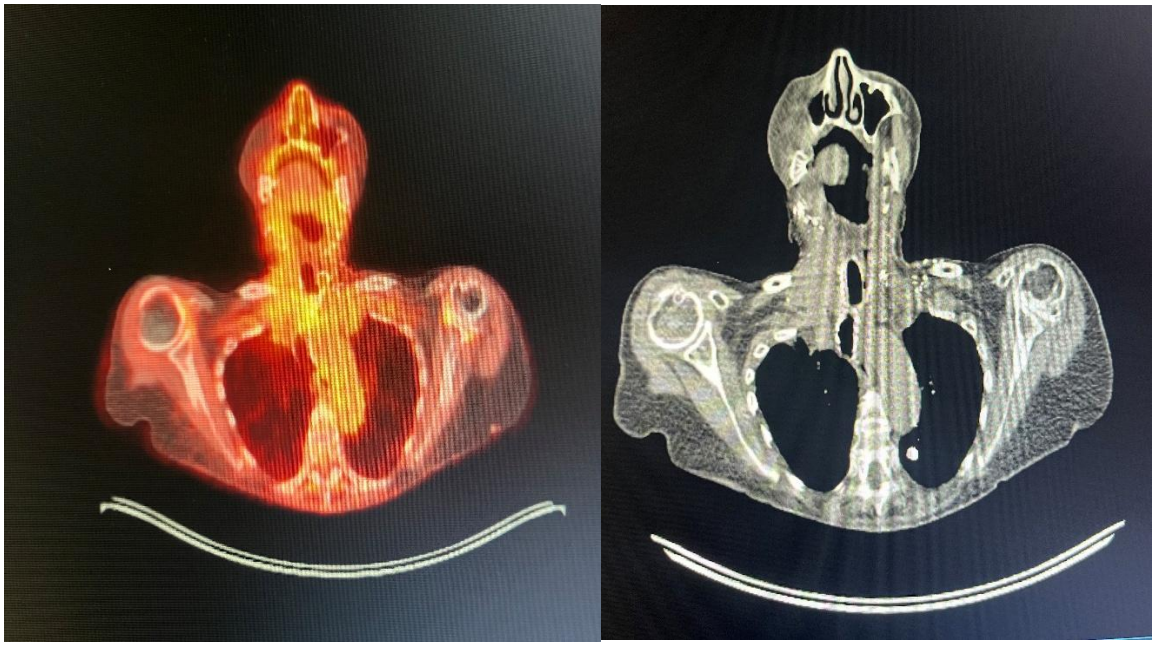

Figure 1 Figure 2

FIG. 1 & 2. **Head and Neck PET/ CT scan showing extensive postoperative changes of laryngectomy and partial phagyngectomy. No bulky adenopathy.**

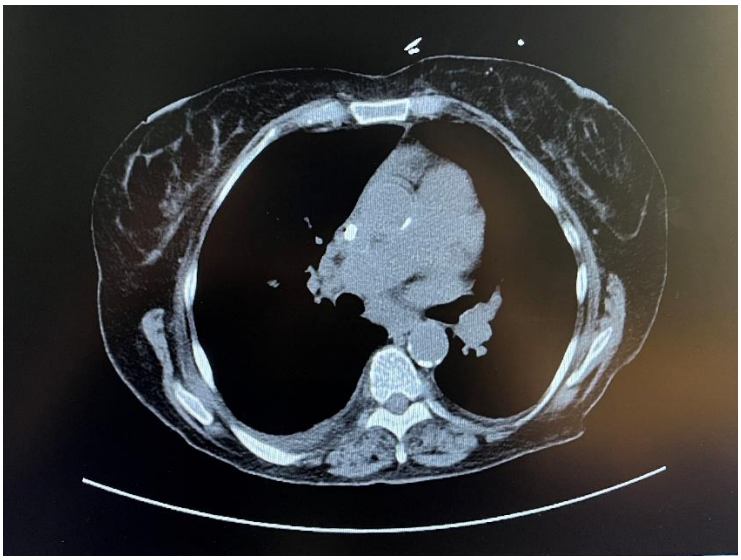

FIG. 3. **CT of the chest showing no pathologically enlarged lymph nodes.**

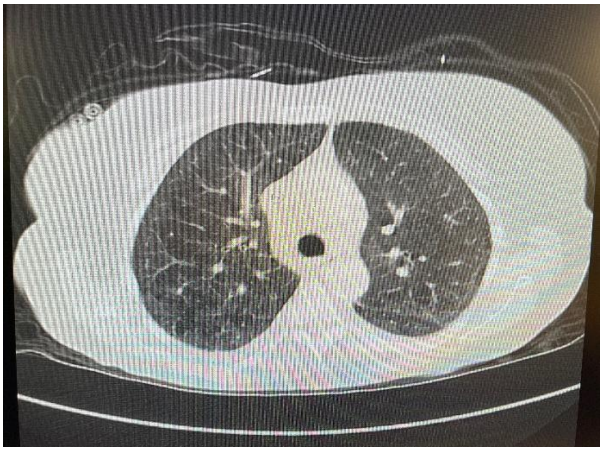

FIG. 4. **CT of the chest showing interstitial and ground glass changes. No pathologically enlarged lymph nodes.**

3. Discussion

Head and neck malignancy and post-surgical- associated hyponatremia and SIADH are multifactorial and can become chronic until tumor burden is controlled. Mild and moderate hyponatremia can cause central nervous system dysfunction due to brain edema, ranging from headache, confusion, dizziness, fatigue, irritability, gait instability, and muscle cramps; while severe hyponatremia can cause severe symptoms such as seizures, coma, confusion, gait disturbances, and osmotic demyelination if corrected too rapidly [1,14,15]. Chronic, often asymptomatic cases in older adults are linked to falls, bone fractures, and cognitive decline [15]. Chronic hyponatremia increases the risk of spine and hip fractures through two primary mechanisms: producing cognitive and gait impairment that leads to falls, and directly increasing bone fragility by inducing bone resorption to mobilize sodium [16,17]. Hyponatremia in oncology patients is also associated with increased mortality, poorer chemotherapy tolerance, cognitive dysfunction, and varied clinical outcomes [18].

Head and neck malignancy and post head and neck surgeries (laryngectomy, thyroidectomy, pharyngectomy) can cause neuroendocrine dysregulations of chronic hyponatremia and SIADH primarily through ectopic arginine vasopressin (AVP) pathway secretion by tumors, or post-surgical disruption of baroreceptor pathways of pituitary of the hypothalamic pathways, persistent V2 receptor activation, aquaporin-2 insertion into collecting ducts, free water retention, or dilutional hyponatremia [11,18-20]. In post-thyroidectomy, SIADH often arises from stress-induced, transient ADH release, particularly following rapid thyroid hormone withdrawal for radioactive iodine (RAI) therapy [20-22]. Chronic inflammatory signaling and cytokine-mediated AVP stimulation (IL-6 mediated) have also been implicated in postoperative SIADH [23-27].

Hyponatremia and SIADH are often triggered by chemotherapy (vinca alkaloids, platinum compounds, and alkylating agents), radiotherapy-induced thyroid dysfunction, or neuroendocrine changes from tumor growth [7,27]. Chemotherapeutic agents can directly cause SIADH through toxicity on hypothalamus neurons [28]. Direct effects of chemotherapeutic agents and obstruction of cerebral blood flow induced by radiotherapy, leading to increased AVP production, have been proposed as possible mechanisms [28]. Radiation to the neck frequently induces hypothyroidism, a known cause of hyponatremia and SIADH [29]. Radiation can also cause cerebral vasculopathy, leading to AVP release via radiation-triggered endothelial cell apoptosis and senescence, disrupting normal vascular homeostasis and signaling cascades, and resulting in vessel wall thickening, fibrosis, and eventual stenosis or occlusion, as well as endocrine abnormalities [30,31].

Managing chronic hyponatremia and SIADH after head and neck cancer surgery or post-thyroidectomy requires a cautious approach, as these patients are prone to severe, often asymptomatic, euvolemic hyponatremia due to surgical stress, pain, or thyroid hormone withdrawal [32,33]. The cornerstone of management is identifying the underlying cause, such as stopping offending drugs, increasing protein intake and use of urea or salt tablets, replacing thyroid hormone, and gradually correcting sodium to avoid Osmotic Demyelination Syndrome (ODS), with a max correction of 10-12 mmol/L in 24 hours [32,33]. When hyponatremia is caused by SIADH, hypertonic saline is indicated for acute symptomatic cases, whereas fluid restriction is recommended in chronic asymptomatic hyponatremia [31].

4. Therapeutic Role of Tolvaptan

Tolvaptan is an oral, selective vasopressin V2-receptor antagonist that promotes aquaresis by blocking antidiuretic hormone (ADH) action in the renal collecting ducts [34]. It has linear pharmacokinetics (15 mg - 60 mg), a half-life of 6-8 hours, 98% protein binding, hepatic CYP3A4 metabolism, and minimal renal excretion of unchanged drug [32-35]. The recommended starting dose is 15 mg daily, titrated to 30 mg - 60 mg based on sodium response [32-35]. Fluid restriction should be avoided during correction [33,34]. Serum sodium must be monitored every 4-6 hours due to the risk of overly rapid correction and osmotic demyelination syndrome (ODS) [32-35]. Liver toxicity is a major concern, especially with prolonged use (notably from the TEMPO trial), and therapy is generally limited to 30 days per FDA guidance [34]. Common adverse effects include thirst, dry mouth, polyuria, and dizziness [34]. It is contraindicated in hypovolemic hyponatremia, anuria, impaired thirst, pregnancy, and severe symptomatic hyponatremia requiring hypertonic saline [34].

Clinical trials (SALT-1, SALT-2, SALTWATER) demonstrated significant improvement in serum sodium in euvolemic and hypervolemic hyponatremia, including SIADH [36,37]. Limited cancer-specific data suggest benefit in lung cancer–associated SIADH, including improved sodium levels, ECOG status, and facilitated chemotherapy [32,38]. Short-term adherence is good (70–90%), though long-term compliance declines [36]. Overall, tolvaptan is effective and generally well tolerated, but requires close monitoring for hepatotoxicity and rapid correction of sodium levels.

5. Conclusion

This case emphasizes the clinical challenge of managing the high recurrent burden of SIADH in a patient with head and neck malignancy and post-surgical- associated hyponatremia and SIADH. Malignancy-associated SIADH represents a serious and recurrent cause of profound hyponatremia. It demonstrates that low-dose tolvaptan may serve as an effective therapeutic choice for refractory SIADH. However, the cost of tolvaptan could be a barrier for outpatient settings. Early recognition and individualized therapy are essential to prevent neurologic complications and reduce the risk of repeated hospitalizations.

6. Contributors

The authors wrote and edited the manuscript. The authors approved the final version of the manuscript and are responsible for all aspects of this study.

7. Competing Interests

None stated.

8. Funding

None.

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