

# Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) Associated with Mediastinal Schwannoma

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Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause of euvolemic hypo-osmotic hyponatremia. There are several etiologies of SIADH including neuroendocrine tumor, pulmonary disease, infection, trauma, and medications. Here, we report a case of SIADH associated with a schwannoma involving the mediastinum in a 75-year-old woman who presented with nausea, vomiting, and general weakness. Laboratory testing showed hypo-osmolar hyponatremia, with a serum sodium level of 102 mmol/L, serum osmolality of 221 mOsm/kg, urine osmolality of 382 mOsm/kg, urine sodium of 55 mmol/L, and plasma antidiuretic hormone (ADH) of 4.40 pg/mL. Chest computed tomography identified a 1.5-cm-sized solid enhancing nodule in the right lower paratracheal area. A biopsy specimen was obtained by video-assisted thoracoscopic surgery, which was diagnosed on pathology as a schwannoma. The hyponatremia was completely resolved after schwannoma resection and plasma ADH level decreased from 4.40 pg/mL to 0.86 pg/mL. This case highlights the importance of suspecting and identifying the underlying cause of SIADH when faced with refractory or recurrent hyponatremia, and that on possibility is mediastinal schwannoma

**Key Words:** Hyponatremia, Syndrome of Inappropriate ADH (SIADH) Secretion, Mediastinal schwannoma

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## Introduction

Hyponatremia (serum sodium concentration <135 mmol/L) is the most common electrolyte disorder encountered in clinical practice<sup>1</sup>. It is important to recognize hyponatremia, as it is associated with potential mortality and can also be a sign of underlying disease<sup>2</sup>. The most common cause of hyponatremia is syndrome of inappropriate antidiuretic hormone secretion (SIADH), in which arginine vasopressin is secreted independent of plasma osmolality<sup>1</sup>. In the elderly, 51 to 58% of cases of hyponatremia are due to SIADH<sup>3,4</sup>. SIADH has many causes, including parane-

oplastic effect of malignant disease, pulmonary disease, disorders of the central nervous system, and medications<sup>2</sup>. Neurogenic tumors are a well-known but rare cause of SIADH. Schwannomas are benign peripheral nerve neoplasms, represent the most common mediastinal neurogenic tumors, and rarely degenerate into malignant disease of nerve sheath origin<sup>5</sup>. Although schwannomas are associated with hyponatremia<sup>6,7</sup>, there was no report to measure and compare changes in plasma ADH concentration. Here, we report a case of SIADH caused by a mediastinal schwannoma that resolved following complete resection.

## Case Report

A 75-year-old woman was referred to our hospital for epigastric pain, nausea, vomiting, and general weakness over 10 days. The patient's mental status was drowsy, but her neurological examination was within normal limits. Her blood pressure was 140/80 mmHg with a pulse rate of 79 beats/min. Her tongue was not dehydrated, skin turgor was normal, and she had no pitting edema. She had no complaints of symptoms such as thirst, polydipsia, or polyuria.

The patient's past medical history was significant for hypertension and a lumbar spine operation in 2004. She had no history of liver disease, heart disease, tuberculosis, syphilis, or radiation therapy. Her medications consisted of anti-hypertensive medication of hydrochlorothiazide 25 mg. In addition, due to bilateral leg pain following her spinal operation, she was taking non-steroidal anti-inflammatory drugs (NSAIDs).

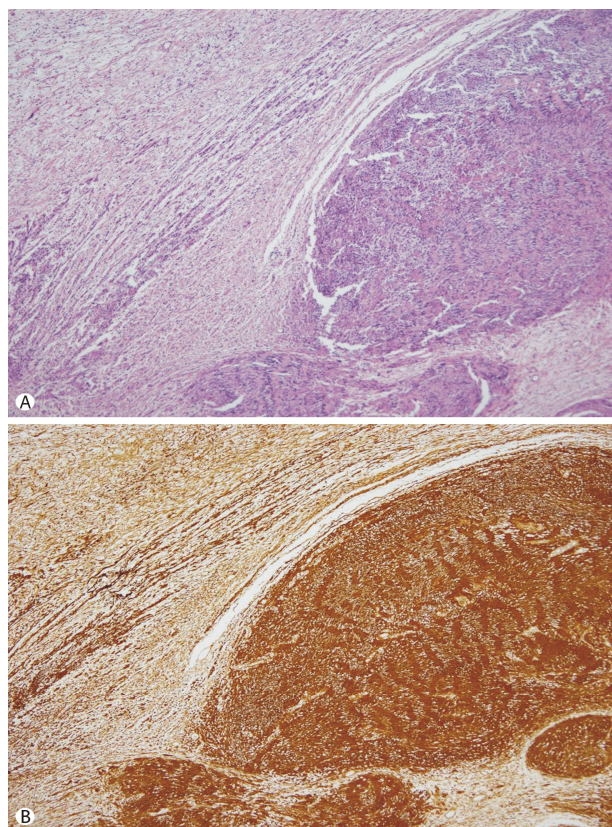
The results of a complete blood count, creatinine, urea nitrogen, protein, and albumin were within normal ranges. The patient was found to have hypo-osmolar hyponatremia with increased urinary sodium excretion and hypouricemia; serum sodium, 102 mmol/L; serum potassium, 2.7 mmol/L; serum chloride, 70 mmol/L; serum uric acid, 2.7 mg/dL; serum osmolality, 221 mOsm/kg; urine osmolality, 382 mOsm/kg; urinary sodium, 55 mmol/L; urinary potassium, 43.1 mmol/L; and urinary chloride, <60 mmol/

L; FENa, 0.91%. Urinalysis revealed trace (+/-) hematuria and proteinuria. Her thyroid function test showed T3, 69 ng/dL; T4, 1.52 ng/dL; and TSH, 3.61 uIU/mL. The patient's plasma adrenocorticotropic hormone (ACTH) level was 5 pg/mL, and she had a normal response to a rapid ACTH stimulation test. Her plasma ADH level was increased to 4.40 pg/mL.

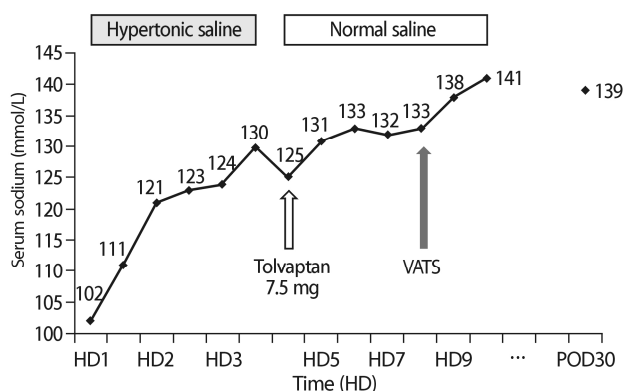
The patient's serum sodium concentration increased from 102 to 130 mmol/L following an intravenous infusion of hypertonic saline (3.0% NaCl) and discontinuation of possible causative medication (hydrochlorothiazide). However, after discontinuation of hypertonic saline, the patient's serum sodium level again decreased to 125 mmol/L. We used a tolvaptan, a selective vasopressin receptor 2 antagonist, 7.5 mg (one quarter 30 mg tablet) once a day under the diagnosis of SIADH because of inappropriately increased ADH level. On the first day of administration,



**Fig. 1.** Enhanced chest computed tomography. A hyper-attenuated solid enhancing nodule can be seen in the right lower paratracheal area (arrow)



**Fig. 2.** Microscopic images of the mediastinal schwannoma. (A) Markedly increased cellularity and fascicles of spindle cells in a loose stroma (hematoxylin and eosin staining, 40 $\times$ ). (B) Immunohistochemical analysis showing diffuse strong positivity for S-100 (40 $\times$ ).



**Fig. 3.** Serum sodium level of the patient during hospitalization. The sodium level recovered during infusion of hypertonic saline, but decreased after discontinuation of hypertonic saline. The patient's serum sodium was completely recovered after schwannoma excision by VATS. HD, hospital day; POD, post-operative day; VATS, video-assisted thoracoscopic surgery.

the sodium concentration temporarily increased to 132 mmol/L. But the patient complained of polyuria and thirst, so we stopped using the drug. In order to identify the cause of SIADH, we conducted brain magnetic resonance imaging (MRI), chest computed tomography (CT), and abdominal-pelvic CT. There were no specific lesions identified on brain MRI or abdominal-pelvic CT, whereas chest CT revealed a 1.5-cm-size solid enhancing nodule in the right lower paratracheal area as well as nodules in both lobes of the thyroid gland. A subsequent anterior thyroid scan with T-99m pertechnetate revealed small hot nodules in both thyroid lobes. The results of an ultrasound-guided fine needle aspiration of the thyroid nodules were benign, and there was no endobronchial lesion on bronchoscopy. Video-assisted thoracoscopic surgery (VATS) was then performed to evaluate the mediastinal lesion. Gross examination of the specimen showed a well-capsulated, round, hemorrhagic mass, measuring 4.3×2.3×1.2 cm. Microscopic examination revealed markedly increased cellularity and elongated spindle cells associated with a storiform pattern. Immunohistochemical study showed S-100 positivity. Based on these findings, the patient was diagnosed with schwannoma, and her hyponatremia improved and antidiuretic hormone level decreased from 4.40 pg/mL to 0.86 pg/mL after excision of the mass.

On the 30<sup>th</sup> day after the removal of schwannoma, the patient's sodium level was checked as 139 mmol/L at the

outpatient clinic.

## Discussion

Hyponatremia is a common but critical electrolyte disorder seen in clinical practice, of which SIADH is the most frequent cause<sup>2</sup>. There are several causes of SIADH, which can be categorized as a paraneoplastic effect of malignant disease, pulmonary disease, disorders of the central nervous system, and medications<sup>2</sup>. SIADH patients have clinical euvolemia since there is no impairment in volume regulatory hormones (aldosterone and natriuretic peptides)<sup>2,8</sup>. Essential to diagnosing SIADH is both the low plasma osmolality and the urine osmolality exceeding 100 mOsm/kg<sup>2,9</sup>. In SIADH patients, it is important to rule out other potential causes of euvolemic hypoosmolality including severe hypothyroidism and glucocorticoid insufficiency<sup>2,9</sup>.

Our patient's laboratory findings were consistent with a diagnosis of SIADH; however, we did not rely on urine sodium because she was taking hydrochlorothiazide and NSAIDs. Indeed, while use of a thiazide or NSAID is a common cause of hyponatremia, we suspected another cause in our patient due to the persistence of symptoms after cessation of these medications. In addition, there were no specific abnormalities on the thyroid function test or ACTH stimulation test, further supporting a diagnosis of SIADH. Finally, we conducted various imaging studies to identify the potential cause of the patient's SIADH. We identified a right lower paratracheal lesion on chest CT, which was extracted by VATS and histologically confirmed as a schwannoma.

Schwannomas are a neurogenic tumor and are the most common benign tumor of the posterior mediastinum<sup>5,10</sup>. Schwannomas originate from Schwann cells and are thus ectodermal in origin<sup>11</sup>. Schwannomas frequently arise from spinal nerve roots, but can involve any thoracic nerve<sup>12</sup>. The peak incidence of schwannoma is in the 3<sup>rd</sup> and 4<sup>th</sup> decades of life, with an equal number of cases in men and women<sup>5,13</sup>. Schwannomas grow very slowly and rarely transform to malignant disease<sup>5</sup>. Most patients are asymptomatic, but some can develop pain or paralysis due to enlargement of the tumor and compression of adjacent

structures. Surgical removal is the treatment of choice, which prevents further growth and compression on surrounding tissues<sup>13-15</sup>.

Some studies have reported that hyponatremia associated with schwannomas is due to adrenal insufficiency and panhypopituitarism caused by intra- and suprasellar schwannoma<sup>6,7</sup>. Pitale et al. reported the case of a 72-year-old man with hyponatremia accompanied by bitemporal visual field defects caused by an intra- and suprasellar schwannoma<sup>6</sup>. Likewise, Bernreuther et al. reported the case of a 61-year-old man with hyponatremia and neurological symptoms also resulting from an intra- and suprasellar schwannoma<sup>7</sup>. In both of these reports, the associated hyponatremia was resolved after eliminating the mass. In addition, a number of cases of mediastinal schwannoma have been reported<sup>14,15</sup>; however, none of these reported cases have been associated with hyponatremia or SIADH.

Thus, to the best of our knowledge, this is the first case report of a mediastinal schwannoma associated with hyponatremia or SIADH. Although it remains unclear whether schwannomas are a bystander or a causative factor of hyponatremia, we considered the schwannoma as the cause of SIADH in our case for several reasons. First, previous studies have shown that hyponatremia can be associated with intra- and suprasellar schwannoma<sup>6,7</sup>. Second, beyond the schwannoma, we did not observe any other malignancy, pulmonary disease, or disorder of the central nervous system in our patient. Likewise, tumor markers and other imaging studies were negative, including abdominal-pelvic CT, brain MRI, thyroid ultrasonography and scan, breast ultrasonography, esophagogastroduodenoscopy, and bone scan. Thirdly, the patient's hyponatremia was resolved after eliminating the schwannoma and did not recur even without active treatment (3% saline or tolvaptan). Fourthly, we believe that the rapid decrease in ADH concentration right after excision strongly supports Schwannoma as a direct cause of SIADH. But, it is a limitation of this case that we didn't perform the immunohistochemical staining for arginine vasopressin in mediastinal schwannomas.

In conclusion, we reported an unusual case of severe hyponatremia associated with a mediastinal schwannoma, although the pathophysiology of SIADH induced by the

schwannoma in our patient remains unclear. Nevertheless, it is important for physicians to investigate the underlying cause of refractory or recurrent hyponatremia, as it can be a marker of underlying disease. Especially, we emphasize that schwannomas are a potential cause of SIADH and should be included in the differential diagnosis of SIADH.

### Conflicts of interest

The authors have no conflicts of interest to declare.

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