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Primary central nervous system lymphoma with initial presentation of cerebral salt-wasting syndrome shifting to syndrome of inappropriate antidiuretic hormone secretion: A case report

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ABSTRACT

Background. Primary central nervous system lymphoma (PCNSL) is a rare form of non-Hodgkin lymphoma which may affect brain parenchyma. Hyponatremia can be present as one of the complications, either due to neuronal injury arising from in-situ tumor and/or surgical resection (resulting in cerebral salt wasting syndrome/CSWS) or indolent, slowly progressing and often asymptomatic one as a consequence of ongoing chronic illness (so-called syndrome of inappropriate antidiuretic hormone/SIADH). Differentiating between the two is critical, since each diagnosis has a starkly different treatment approach which may exacerbate one another.

Case presentation. Herein, we reported a case of a 48-year-old immunocompetent male who presented with diplopia, hallucination, imbalance, and dizziness, later to be diagnosed with PCNSL on multiple brain regions. He suffered from symptomatic hyponatremia post-surgically as a result of CSWS which in turn responding well to intensive dose of desmopressin acetate and fluid replenishment. However, as the disease progressed, hyponatremia also relapsed but was refractory to the same treatment approach. After subsequent investigations, patient was known to have SIADH. Treatments tailored to SIADH including fluid restriction and administration of hypertonic saline as well as tolvaptan lead to stabilization of sodium levels and significant clinical improvements.

Conclusion. Post-operative hyponatremia in the setting of a PCNSL continues to be a complex issue. It underscores the importance of careful clinical assessment, monitoring, and the need for flexibility in diagnosis and management strategies. Furthermore, it highlights the challenges of distinguishing between CSWS and SIADH, two conditions with similar laboratory findings but divergent management approaches. Recognizing the subtleties in clinical presentation and responding appropriately can greatly influence patient outcomes. The rising incidence of PCNSL in immunocompetent individuals also needs a heightened awareness and understanding of its presentations and potential post-operative complications among clinicians.

Keywords: PCNSL, CNS malignancy, immunocompetent, SIADH, CSWS

List of abbreviations

ADH	– Anti diuretic hormone	HIV	– Human immunodeficiency virus
AVP	– Arginine vasopressin	ICU	– Intensive care unit
CBNP	– Brain natriuretic peptide	NT-proBNP	– N-terminal prohormone of brain natriuretic peptide
CNS	– Central nervous system	PCNSL	– Primary central nervous system lymphoma
CSWS	– Cerebral salt-wasting syndrome	SAH	– Subarachnoid hemorrhage
CT	– Computed tomography		
CVP	– Central venous pressure		

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SIADH – Syndrome of inappropriate antidiuretic hormone
TBI – Traumatic brain injury
TSH – Thyroid stimulating hormone

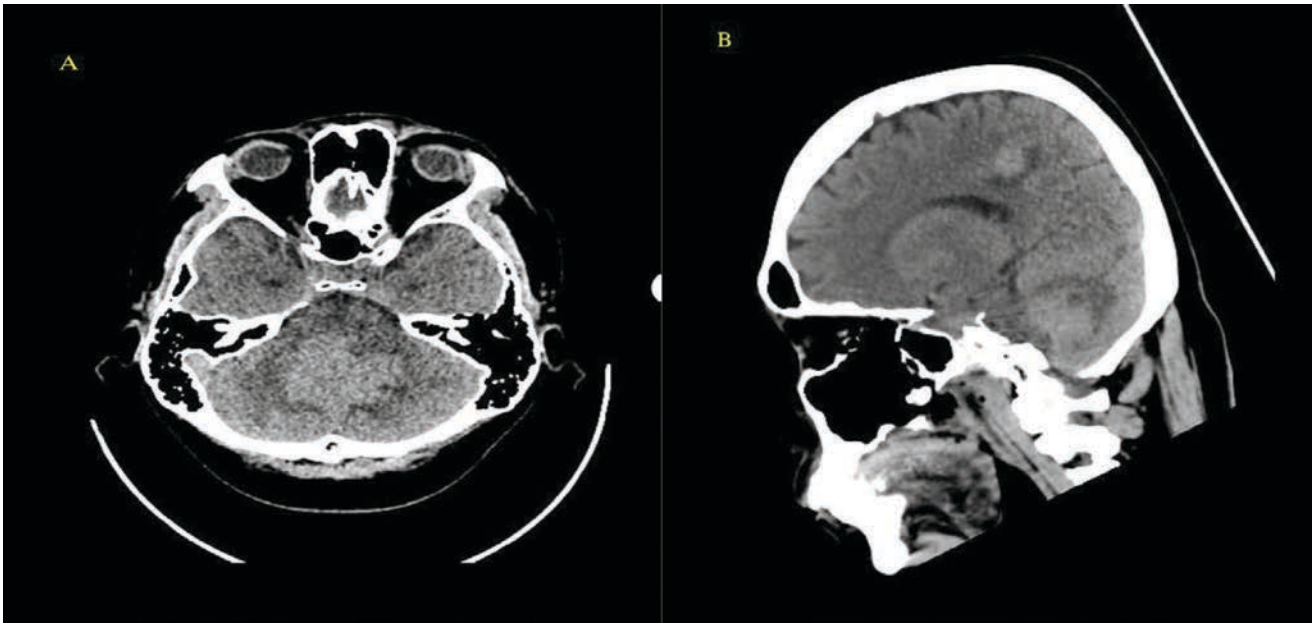

FIGURE 1. CT scan (axial view) (A) showing hyperdense lesion in the fossa posterior with (B) another hyperdense nodule in the subcortical area of the right parietal region

INTRODUCTION

PCNSL is a form of non-Hodgkin lymphoma that originates within the brain parenchyma, spinal cord, eyes, and cerebrospinal fluid without evidence of systemic involvement. The majority of PCNSL are the diffuse large B-cell type [1-3]. PCNSL represents approximately 1% of all lymphomas and approximately 1%–4% of all CNS malignancies. The incidence appears to be increasing, especially among immunocompetent patients. However, the exact reason for this rising incidence of PCNSL among the immunocompetent population is still unknown [1,2]. The treatment of PCNSL has evolved over the years. The goal of therapy is to achieve a complete response while minimizing long-term neurotoxicity [4,5]. Post-operative hyponatremia complications that may arise are CSWS and SIADH [6]. CSWS is characterized by renal loss of sodium, leading to hyponatremia and hypovolemia. It has been primarily linked with conditions like subarachnoid hemorrhage but has recently been identified in patients with brain tumors, including PCNSL On the other hand, SIADH, a condition characterized by inappropriate secretion of antidiuretic hormone leading to hyponatremia and sometimes fluid overload, has been documented in various malignancies [6-8].

Differentiating between these two conditions is crucial given the diametrically opposite treatment approaches. While CSWS requires sodium and fluid replacement, SIADH necessitates fluid restriction [6-8]. Proper diagnosis and management of complications like CSWS and SIADH are crucial for optimizing patient outcomes. Herein we described an immunocompetent patient who had PCNSL and developed serial hyponatremia after resection of the tumor.

CASE REPORT

A 48-year-old male with no history of HIV or autoimmune disease presented to the neurosurgery clinic with diplopia, hallucination, imbalance, and dizziness lasting for three weeks. Patient was found to have dysarthria, a left facial droop, and gait ataxia. Signs and symptoms of increased intracranial pressure (e.g. headaches, nausea, vomiting, or papilledema) were absent. Subsequent non-contrast CT of the brain showed a lobulated midline hyperdense mass in the posterior fossa with perifocal edema compressing the fourth ventricle and posterior pons. No obstructive hydrocephalus was found on the current CT (Figure 1). Another hyperdense nodule was found in the subcortical area of the right parietal region, accompanied by surrounding edema.

No abnormalities were detected on complete blood count, liver and kidney function tests, electrolytes, coagulation function, hepatitis B and HIV virus marker. CT scan of the chest and abdomen were within normal limits. The patient underwent craniotomy and tumor resection. Pathology examination demonstrated monotonous, diffuse round nuclei, with scant cytoplasm, high N/C ratio, hyperchromatic, numerous mitosis, and lots of apoptotic debris sug-

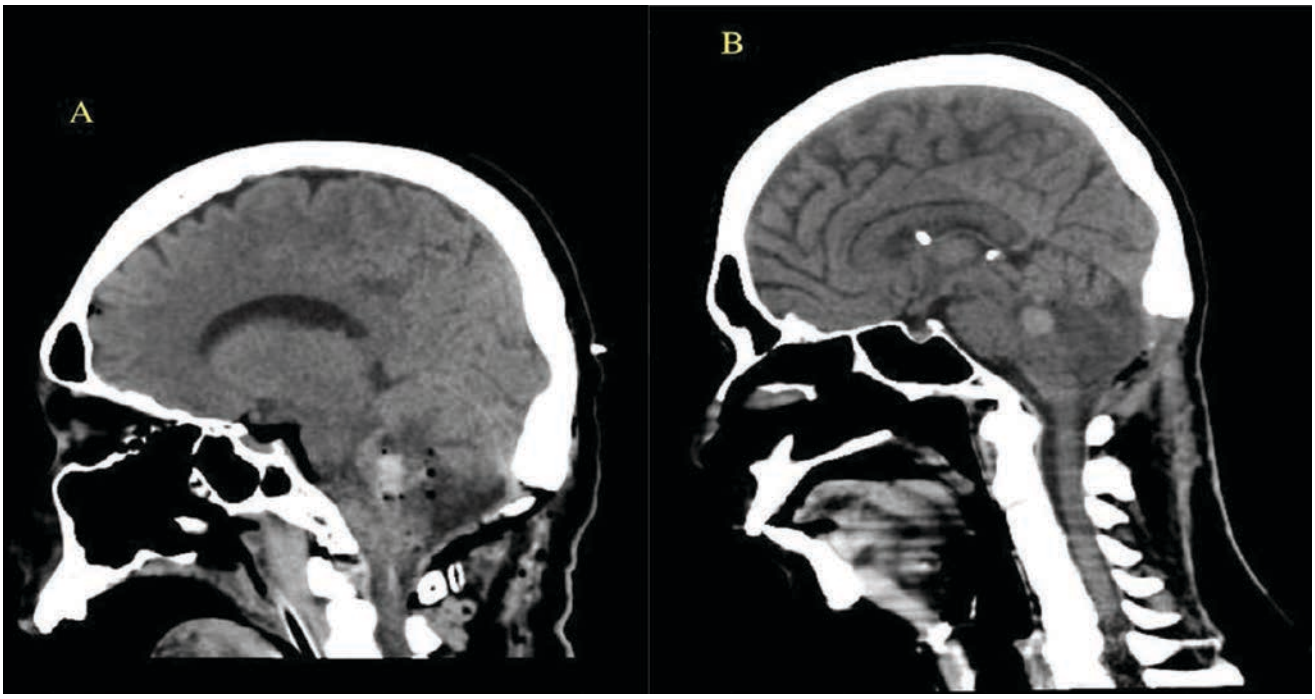

FIGURE 2. CT scan sagittal view showing (A) lobulated midline hyperdense mass in the posterior fossa mostly had been evacuated while (B) readmission CT scan revealed a hyperdense rounded nodule in surgical bed at the posterior fossa, suggested to be a recurrent mass lesion

gesting Non-Hodgkin Lymphoma. Immunohistochemistry for CD20, CD10, BCL6, MUM-1, and KI-67 (90%) were positive on viable tumor cells, but negative for CD3 and Cyclin D1. Following surgery, our patient underwent chemotherapy with a regimen of rituximab and temozolomide (i.e. 500 mg of rituximab on the first day, followed by 200 mg of temozolomide for 5 days).

At 48 hours post-surgery patient presented with decreased of consciousness and polyuria wherein urine production exceeded 200 ml/h. Patient appeared dehydrated with low central venous pressure, whereas subsequent follow-up CT scan demonstrated neatly evacuated tumor with no visible hydrocephalus (Figure 2A). However, severe hyponatremia (117.4 mmol/L) in the presence of low plasma osmolality (247.74 mOsm/kg) and markedly elevated urine sodium levels (603.6 mEq/L) were identified, leading to a diagnosis of CSWS, thought to be post-operative complications. Hypertonic saline 3% and normal saline were given to correct the hypovolemic hyponatremia. In spite of fluctuating sodium levels, (i.e. 127, 124.4, and 126 mmol/L) patient appeared to respond well to treatment and was discharged 2 weeks later.

Four weeks following the surgery, our patient was re-admitted to the hospital with decreased of consciousness, wherein CT scan revealed a hyperdense rounded nodule in surgical bed at the posterior fossa, thought to be a recurrent mass lesion, and another nodule in the right parietal region relatively bigger in size compared to the last CT scan, accompanied by diffuse edema (Figure 2A and 2B).

Hyponatremia persisted despite sodium and fluid correction (Figure 2A and 2B for comparison). Patient's urine output decreased (Figure 3), and his condition seemed clinically worsened. N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was within normal limits accompanied by hypouricemia (148.7 μmol/L). Thyroid and early morning cortisol tests were done and within normal range. Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) was suspected to be the cause of post-operative hyponatremia (see comparisons on Table 1). Our patient underwent fluid restriction of 1.5 L/day for 3 days, and tolvaptan 15 mg qd was administered. Within three days the patient's consciousness began to improve with significant increment of serum sodium levels (from 128 mmol/L to 132 mmol/L) and decreased urinary sodium levels (from 606.7 mEq/ to 303.5 mEq/L). Our patient was discharged with serum sodium levels of 136.7 mmol/L and remained stable thereafter.

TABLE 1. Comparison of patient's hyponatremia post-operatively and upon re-admission

	Post-Operative	**Re-admission**
Serum sodium	Hyponatremia	Hyponatremia
Urinary sodium	Increased	Increased
Volume status	Hypovolemia	Euvolemia
Urine output	>4L/day	0.7-1.5L/day
Treatment	Fluid and sodium replacement	Fluid restriction + tolvaptan

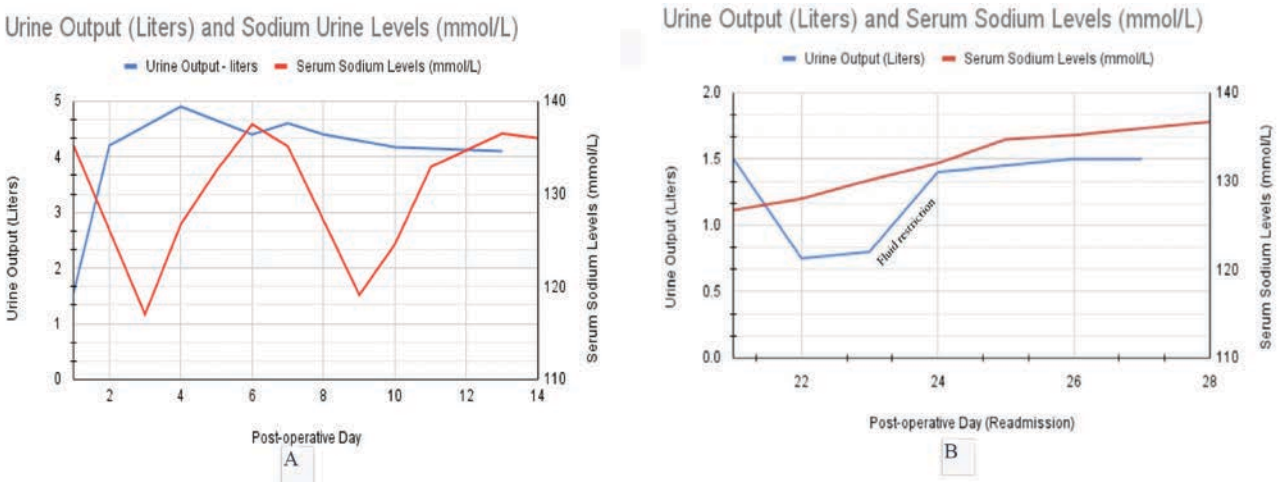

FIGURE 3. Relationship between urine output and serum sodium post-operatively (A) and during hospital re-admission (B)

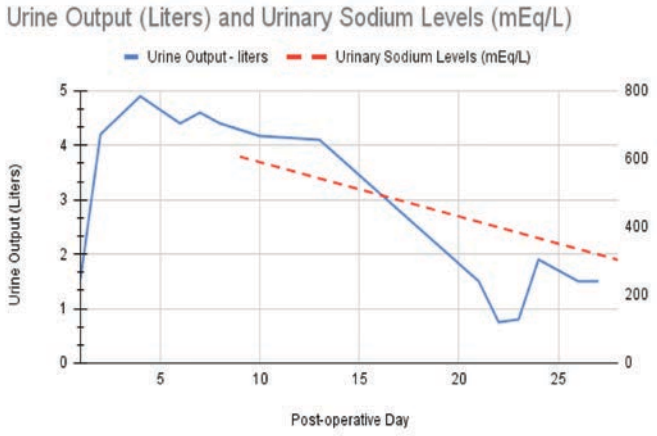

FIGURE 4. Relationship between urine output and urinary sodium post-operatively and after hospital re-admission

DISCUSSION

PCNSL is a relatively rare form of non-Hodgkin lymphoma. Its prevalence varies across different populations and regions. Our patient is a 48-year-old male with no history of HIV or autoimmune diseases. Among immunocompetent population, PCNSL mostly occurs in 65+ years old, with incidence has been rising over the past few decades. Improved diagnostic techniques or a true rise in incidence could contribute to this trend [1-2]. More than 90% of PCNSL are diffuse large B cell lymphoma (DLBCL). Other less common types of PCNSL include T-cell lymphomas and Burkitt lymphoma.

The incidence of hyponatremia is between 8 and 35% in brain tumors [7,9]. The exact percentage might vary depending on the type and location of the tumor. Hyponatremia can be related to various brain tumor locations, but it's most frequently associated with tumors affecting the pituitary gland and hypothalamus (i.e. pituitary tumor, craniopharyngioma with suprasellar extension) [7-10]. Common mechanisms of brain tumor related to hyponatremia are various including the SIADH, CSWS, adrenocorticotropic hormone deficiency, or other factors related to the tumor or its treatment [6-10]. In patients admitted to neurosurgical units with intracranial tumors and hematomas and in patients undergoing pituitary surgery, hyponatremia occurs in between 10% and 20% of patients [11,12]. The majority of available research focuses on pituitary tumors. Hyponatremia is less commonly observed in supratentorial tumors (after excluding sellar/suprasellar tumors) compared to traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), and pituitary tumors [12,21]. Patients who underwent transsphenoidal surgery found a postoperative hyponatremia incidence ranging from 4% to 12% [13].

Our patient developed hyponatremia (117 mmol/L) and massive urine excretion >200 ml/h with signs of dehydration (decreased skin turgor, dry mucous membrane) and low CVP indicated hyponatremia with hypovolemia. CSWS which is a rare condition characterized by excessive loss of sodium in the urine, leading to hyponatremia and hypovolemia was thought to be post-operative complications. CSWS ordinarily occurs after severe brain injury, severe cerebrovascular disease, or surgery [14]. One retrospective cohort study from a single institution showed five percent (15 of 291) of pediatric brain tumor patients developed CSWS in the postoperative period. Median onset of CSWS, defined as time between surgery and the first low serum sodium value, occurred on post-operative day 3 (range, 0–24 days) [15,25].

The patient must be adequately hydrated while treating the low sodium levels. Hypertonic saline 3% and normal saline were given to our patient to correct the hyponatremia and hypovolemia. Usually, the patient is initiated on an isotonic saline solution for mild to moderate cases of low sodium levels due to CSWS. The balanced fluid should replenish for patient's low sodium and volume conditions. In the case of moderate to severe cases of low sodium levels,

more aggressive sodium replenishment may be necessary with either a concentrated saline solution such as 3% concentrated saline and/or sodium tablets (1 to 2 grams up to three times daily) [6,7]. Sodium serum levels were closely monitored to avoid both overcorrection, which may lead to nausea, headache, altered consciousness, seizure, and death or overly rapid correction, which may result in osmotic demyelination syndrome.

Four weeks following the surgery, the patient was readmitted to the hospital with decreased of consciousness wherein CT scan revealed a hyperdense rounded nodule in the surgical bed at the posterior fossa suspected to be a recurrent mass lesion. Relapse rates have been noted to be around 30-60% or even higher in some studies, and most relapses occur within the first two years after diagnosis [16-18].

Patient's urine output was decreased which patient's fluid status was euvolemic whereas patients with CSWS typically have a reduced effective circulating blood volume (hypovolemia) [6,14,15]. Further investigations such as NT-proBNP value, thyroid function, cortisol test, and uric acid were done. NT-proBNP value was within normal limits. An elevated BNP or NT-proBNP in the context of clinical features consistent with CSWS might suggest the presence of hypovolemia. Uric acid test showed hypouricemia. Thyroid-stimulating hormone (TSH), free T4 and early morning cortisol tests were within normal limits. Based on patient's current clinical status (hyponatremia with euvolemia), another cause of post-operative hyponatremia was evaluated. SIADH, which is a condition where inappropriate secretion of ADH from the pituitary gland or nonpituitary sources leads to water retention and dilutional hyponatremia was thought as another cause of post-operative hyponatremia [8-10]. Our patient underwent fluid restriction 1.5 L/day for 3 days and medication like tolvaptan 15 mg was administered. The decision to fluid restrict was based on the aim of preventing further dilution of serum sodium and encouraging the body to naturally excrete excess water. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, was initiated. Tolvaptan acts by inhibiting the action of vasopressin, increasing urine water excretion, thereby correcting the hyponatremia associated with SIADH [6,20,21].

Within three days the patient's clinical condition improved as sodium levels showed significant increment from 128 mmol/L to 132 mmol/L, suggesting a correction of hyponatremia. Urine sodium levels was also decreased to 303.5 mEq/L. Patient's consciousness level significantly improved, as evidenced by an upgrade in the Glasgow Coma Scale from E2 V2 M5 to E4 V4 M6.

To date, there is no definitive test for diagnosing SIADH. Typically, patients display hyponatremia while maintaining a normal volume status. The clinical criteria set by Schwartz and Bartter remains applicable till present [6,22].

An elevated urinary sodium concentration is not specific only to SIADH. It can also be observed in cases where the kidneys are losing solutes due to factors like diuretic medications or a deficiency in mineralocorticoids. Suppose individuals with SIADH experience low blood volume or become deficient in solutes, for instance, through restricting salt and fluid. In that case, their urine sodium concentration might decrease as seen in our patient, sodium urine level became lower 303.5 mEq/L after fluid and salt restriction [6,21].

Besides the diagnostic criteria outlined by Bartter and Schwartz, several other markers have been proposed to help differentiate SIADH from other hyponatremia causes. One such marker is copeptin, a significant segment of the arginine vasopressin (AVP) precursor molecule. Copeptin boasts better stability than AVP, making it simpler to measure. Some researchers believe that the ratio of copeptin to urine sodium can reliably differentiate between hyponatremia due to low blood volume and SIADH.23 This same group of researchers suggests that detecting an increased fraction of uric acid in urine is a strong indicator of SIADH, even for patients taking diuretics. Despite these findings, these diagnostic approaches are not commonly utilized in standard clinical settings.

CONCLUSIONS

Hyponatremia in patients with brain tumor remains a complex issue that emphasizes the necessity for detailed clinical evaluation, adaptable diagnostic, and management plans. Various mechanisms can be associated to hyponatremia leading to the difficulty of differentiating between CSWS, SIADH, or any other conditions causing hyponatremia. Both SIADH and CSWS have similar laboratory results but require different treatments. Detecting the nuanced differences in clinical signs and taking the appropriate treatment strategies can significantly impact patient outcome. Given the increasing occurrence of PCNSL in those with normal immune systems, there is a pressing need for medical professionals to be more aware of its symptoms and potential post-operative complications.

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