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CASE REPORT

Case Report: Hyponatremia of malignancy – An alternative mechanism? Syndrome of inappropriate atrial natriuretic peptide (SIANP) [version 1; peer review: 2 not approved]

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Abstract

Euvolemic hyponatremia in the setting of lung cancer is most commonly due to the syndrome of inappropriate anti-diuretic hormone secretion (SIADH). However, some patients with small cell carcinoma and hyponatremia have low levels of ADH but elevated levels of atrial natriuretic peptide (ANP), which is produced by some small cell tumors. We report the case of a 64-year-old man with a limited-stage small cell carcinoma of the lung undergoing chemoradiation therapy, who was admitted to hospital with a pulmonary embolism. Two months earlier, at the time of diagnosis with lung cancer, he had a hypotonic, euvolemic hyponatremia, presumed to be caused by SIADH. At that time, his serum sodium readily normalized with water restriction and ADH-antagonist therapy with demeclocycline. However, during his second admission, his sodium level slowly declined from 138 mmol/L to a nadir of 118 mmol/L, despite early initiation of water restriction and maximal doses of demeclocycline. Laboratory values revealed a very low level of ADH, an inappropriately low level of aldosterone and an elevated ANP suggesting that SIADH could not explain his hyponatremia. While a causal link between ectopic ANP production and hyponatremia has never been established, an inappropriately high level of ANP can directly decrease sodium re-absorption in the proximal convoluted tubule of the kidney and increase glomerular filtration rate (GFR), resulting in greater excretion of sodium and water. In addition, high circulating levels of ANP can inhibit aldosterone secretion, potentially resulting in further sodium wasting. Here, the low levels of ADH, elevated ANP, and inappropriately low aldosterone suggested the possibility of an ANP-mediated hyponatremia through the suppression of aldosterone response.

Keywords

ADH, SIADH, ANP, hyponatremia

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Introduction

Hyponatremia is commonly found in patients that have been diagnosed with lung cancer – reportedly as high as 15–30% of patients with small cell lung carcinoma (SCLC) present with hyponatremia^{1,2}. While it is clear that water and sodium homeostasis are abnormal in these patients, the complete pathogenesis controlling the hormonal mechanisms of renal sodium and water re-absorption in malignancy has not yet been completely elucidated. However, SCLC is associated with a variety of paraneoplastic syndromes characterized by the ectopic production of peptide hormones or centrally-active antibodies^{3,4}. The most common of these paraneoplastic phenomena is hyponatremia of malignancy, traditionally thought to be caused by elevated levels of arginine vasopressin (AVP), otherwise known as anti-diuretic hormone (ADH), ectopically produced by the neoplastic cells. Inappropriately elevated ADH levels increase the permeability of water in the cells of the distal tubule and collecting duct of the kidney, increasing water re-absorption and decreasing free water clearance, thus resulting in subsequent hyponatremia. This condition is widely known as the syndrome of inappropriate ADH secretion or SIADH^{2,5,6}, and antineoplastic therapy and methods to correct hyponatremia such as fluid and sodium restriction typically constitute effective treatment strategies.

While SIADH is clearly responsible for the majority of cases of hyponatremia of malignancy, there have been documented cases of SCLC patients with hyponatremia, but with no detectable levels of ADH in their plasma^{7,8} or produced by their cancer cells^{9–11}. These interesting observations led a number of researchers to investigate potential alternative mechanisms to explain the low levels of sodium observed in these cases. An alternative hypothesis based on reports showing ectopic production of atrial natriuretic peptide (ANP) mRNA in tumor lines, would suggest the possibility of an analogous ectopic hormone syndrome: elevated levels of ectopically produced ANP, referred to here as the syndrome of inappropriate ANP or SIANP. This hypothesis has been attractive because ANP is thought to have physiologic effects that promote natriuresis: direct sodium wasting effects on the kidney through ANP receptors, inhibition of renin secretion and inhibition of aldosterone secretion^{12–14}. Despite the evidence for ectopic production of ANP in tumor cell lines, there is no evidence revealing a causal link between ANP and hyponatremia.

Here we report the case of a middle-age man with known small cell carcinoma of the lung, who developed a progressive, profound hyponatremia despite strict fluid restriction and ADH-antagonist therapy. Laboratory analysis revealed elevated urine osmoles, very low levels of ADH, inappropriately low levels of aldosterone, and elevated serum ANP despite no known history of heart failure and no clinical signs of volume overload.

Case description

A 64-year-old man with limited-stage small cell carcinoma of the lung (Figure 1) undergoing concurrent chemoradiation therapy was admitted to hospital with a pulmonary embolism after collapsing en route to his seventh radiation treatment. At the time of admission, he was at 10 days status after his first cycle of carboplatin/etoposide chemotherapy and he had six treatments of radiation therapy. Admission laboratory values were notable only for a leukopenia and a serum sodium level of 138 mmol/L.

Two months earlier, at the time of his small cell lung cancer diagnosis, he presented with an acute onset altered mental status. A work-up revealed a hypotonic, euvolemic hyponatremia (Na^+ 116 mmol/L), with elevated urine osmolality (609 mOsm/Kg) and urine sodium (181 meq/L). He was presumptively diagnosed with SIADH syndrome, and was treated with a mild fluid restriction and ADH antagonist (demeclocycline at 300 mg PO BID) therapy (Figure 2A),

Figure 1. Histology of the patient's right pulmonary lymph nodes. The numerous atypical small cells with minimal cytoplasm are characteristic of metastatic small cell carcinoma. **Inset.** Immunohistochemical staining is positive for the neuroendocrine marker, synaptophysin, further supporting the diagnosis.

Figure 2. Graphical representation of the patient's sodium levels during two hospitalizations. (A) Initial presentation and diagnosis of small cell carcinoma of the lung. **(B)** Two months later during the current hospitalization when he presented to our service. **(A)** At the time of initial hospitalization for altered mental status, the patient was found to have a sodium level of 116 and an elevated urine osmolality (609 mOsm/Kg). Water restriction and demeclocycline treatment resulted in a slow, steady rise in sodium back toward normal, consistent with SIADH. **(B)** On our service, a slow and steady decline in sodium level was observed despite the early initiation of demeclocycline treatment and sodium and fluid restriction (represented by red arrow). Starting on day 3, the patient resumed radiation therapy after going 5 days without receiving radiation. After reaching a minimum of 118 mmol/L, the sodium level began to rise toward normal. AVP, ADH, and aldosterone levels were drawn on day 13, represented by the blue arrow, and revealed an elevated AVP, but low ADH and low aldosterone (Table 1), consistent with hyponatremia due to SIANP but inconsistent with a hyponatremia due to SIADH.

which restored his normal serum sodium levels after < 3 weeks of therapy. Upon discharge from the hospital after his initial diagnosis, he was continued on 300 mg PO BID of demeclocycline, which he was taking at the time of the current admission for the pulmonary embolism. At home, he was not observing a fluid restricted diet.

While in the hospital for treatment of the pulmonary embolism, his sodium level steadily declined from the admission value of 138 mmol/L to 118 mmol/L over 11 days (Figure 2B), despite severe fluid restriction and increases to maximal doses of demeclocycline (600 mg PO BID, initiated at the red arrow in Figure 2B). Of note, his physical exam remained consistent with a euvoletic hyponatremia – he did not have any evidence of jugular venous distention, pulmonary edema or lower extremity edema. His liver enzymes were within normal limits (AST = 22 IU/L, alkaline phosphatase = 88 IU/L, and total bilirubin = 0.4 mg/dL) and his kidney function remained normal (Cr = 0.7 mg/dL). Further, his thyroid stimulating hormone, free T4 and cortisol levels were normal (Table 1), and his urine osmolality (563 mOsm/Kg) and urine sodium (128 mmol/L) remained high. A computed tomography (CT) scan of the brain revealed no evidence of metastatic disease or intracranial hemorrhage.

During the initial period of hospitalization, the patient was not able to undergo radiation treatments – this therapy resumed on hospital day 3 after having gone five full days without a treatment. Starting on hospital day 12, sodium levels began to spontaneously increase, returning to 135 mmol/L by day 15. On day 13, when the sodium levels were at 125 mmol/L, laboratory values were drawn in an attempt to qualify the etiology of the hyponatremia: ADH levels were 1.7 pg/mL (low < 7.0 pg/mL), aldosterone levels were < 3 ng/dL (low < 32 ng/dL) and ANP levels were at 140 pg/mL (normal 20 – 77 pg/mL) (see Table 1). The laboratory results, imaging data, and his physical exam findings suggested that neither SIADH nor any of the other common etiologies (hypovolemia, hypothroidism, adrenal insufficiency, cerebral salt wasting) could explain this patient's hyponatremia. Fortunately for the patient, once his sodium level began to trend upward, it stayed in the normal range for the duration of his hospital stay and was 137 mmol/L on discharge. Successful reversal of the hyponatremia was attributed to

resumption of his radiation therapy with effective treatment of his malignancy.

Discussion

In 1957, Schwartz *et al.* presented the first cases of hyponatremia of malignancy from inappropriate anti-diuretic hormone secretion in two patients with lung cancer who developed low serum sodium levels associated with continued urinary sodium losses¹⁵. The authors correctly postulated that the tumors were producing excessive levels of anti-diuretic hormone (vasopressin) via a feedback-insensitive mechanism, a hypothesis which was later proven^{16–18}. The same group subsequently went on to further characterize the SIADH and proposed three mechanisms which could theoretically explain the ongoing urinary sodium losses⁵: (i) an increase in the glomerular filtration rate leading to an increase in the filtered load of sodium, (ii) a suppression of tubular re-absorption of sodium secondary to expansion of the extracellular fluid volume, and (iii) a suppression of aldosterone secretion as a result of the elevated extracellular fluid volume.

It is well now known that ADH acts primarily to insert aquaporin channels into the apical membrane of the distal tubule and collecting ducts of the kidney, increasing the permeability of these cells to water, and allowing its re-absorption and excretion of concentrated urine^{19–21}. This process results in an ADH-induced water retention; the subsequent volume expansion activates the mechanisms for secondary natriuresis mentioned above, resulting in both a sodium and water loss in an attempt to restore euvoletmia. With chronic SIADH, sodium loss is much more prominent than water retention and hyponatremia ensues. There has been much discussion on the diagnosis, pathophysiology, and management of hyponatremia secondary to SIADH^{2,6}.

However, it is interesting to note that as many as one-third of patients with documented small cell lung cancer and hyponatremia do not have elevated levels of serum ADH or ectopic production of ADH from their tumor cells^{1,7,22,23}, leading some to propose the more appropriate umbrella term syndrome of inappropriate antidiuresis (SIAD), while reserving the term SIADH for only those cases where ADH levels are actually elevated^{6,24}. An alternative etiology for hyponatremia of malignancy in patients without elevated ADH levels includes ectopic production of ANP, as we postulate in the case presented in this report. As mentioned above, there is evidence that ectopic production of ANP can contribute to hyponatremia.

ANP is a 28 amino acid peptide secreted from the atrial myocytes in response to local wall stretch and increased atrial volume, but also found in the hypothalamus, brainstem nuclei, pituitary and vascular tissue, kidney, and adrenal medulla¹². It was identified and characterized after de Bold *et al.* demonstrated that a cardiac extract produced natriuresis in rats²⁵. While the details surrounding all the physiologic roles of ANP are still under discussion, it seems that renal, vascular, and cardiac actions are important in maintaining the body fluid and sodium homeostasis^{12,13}. The physiological effects of ANP are summarized in Figure 3. Overall, the main function of ANP is to counter increases in blood pressure and volume induced by the activation of the renin-angiotensin system. As such, the actions of ANP result in natriuresis.

Table 1. Laboratory data reveal normal free T4, TSH, and cortisol levels. In addition, the low ADH level rules out SIADH while the elevated ANP level and low aldosterone level are consistent with a hyponatremia due to SIADH.

Hospital Day 12	Patient Levels	Normal Levels
ADH (pg/mL)	1.7	Low < 7.0
Aldosterone (ng/dL)	< 3	Low < 32
ANP (pg/mL)	140	20 – 77
Hospital Day 11	Patient Levels	Normal Levels
Free T4 (ng/dL)	1.4	0.7 – 1.7
TSH (uIU/mL)	0.77	0.27 – 4.20
Cortisol (mcg/dL)	10.3	2.3 – 19.4

Figure 3. Diagram outlining the renal hemodynamic functions of ANP that lead to an increase in sodium excretion. In response to local wall stretch and increased atrial volume, atrial myocytes secrete ANP, which dilates smooth muscle and blocks the action of norepinephrine and angiotensin II, causing a prolonged increase in glomerular filtration rate (GFR). This causes afferent arteriolar dilation with or without efferent arteriolar constriction and the increased GFR increases the filtered load of sodium, washing out the sodium gradient. It has also been demonstrated that ANP directly increases renal excretion of sodium, acting through ANP receptors in the kidney at the distal convoluted tubule (DCT) and the collecting duct (CD). ANP also directly decreases production of renin, angiotensin II and aldosterone contributing to hyponatremia through natriuresis, negative sodium balance, and non-osmotic release of arginine vasopressin (AVP) (from decreased intravascular volume).

This is accomplished through three distinct but inter-related mechanisms. First, ANP is known to dilate smooth muscle in arterioles and venules and block the action of norepinephrine, causing vasodilation and increased renal blood flow^{12,13}. This effectively increases the glomerular filtration rate (GFR) in the kidney leading to increases in the filtered load of sodium and subsequent natriuresis¹³. Radionuclide studies performed in humans support these results by showing both a significant decrease in the mean blood pressure as well as an increase in GFR after intravenous infusion of ANP peptide²⁶. Second, ANP acts directly on ANP receptors in the kidney to increase renal excretion of sodium^{9,12}. This is thought to occur via receptor-induced increases in cyclic GMP which directly increases GFR, inhibits secretion of renin, and reduces sodium and water reabsorption in the collecting duct^{9,13}. These data have been supported by experiments in rats that demonstrated that urine flow and sodium excretion decreases while plasma renin increases after administration of antibodies raised against ANP²⁷. Finally, it is thought that ANP directly blocks the production of renin, angiotensin II, and aldosterone, as these hormones showed decreased levels following ANP intravenous infusions^{12,14,28}. Suppression of aldosterone secretion from the adrenal medulla is yet another mechanism by which ANP can contribute to natriuresis and subsequent hyponatremia.

These physiologic effects suggest that ANP could feasibly be implicated in cases of hyponatremia of malignancy without ectopic production of ADH. Further support for this hypothesis arose when researchers demonstrated ectopic production of ANP mRNA in both tumors and tumor cells of patients with hyponatremia of malignancy from small cell carcinoma. This has been shown using a number of techniques including northern blot, PCR, and nuclease protection assays^{1,7,23}, and the ANP peptide itself has been detected in small cell lung cancer tumors^{7,22,29,30}. Further, there are reports of the resolution of clinical hyponatremia following surgical resection

of an ANP expressing tumor²². Interestingly, plasma levels of ANP have also been found to be elevated in patients with lung carcinoma and elevated plasma levels of ADH^{1,22,30}. A recent case report presented a patient with SCLC, elevated levels of ANP, and elevated levels of ADH that varied in an oscillatory manner³¹.

Despite the reports demonstrating the association of ectopic ANP production and hyponatremia, there is still not overwhelming evidence proving a causal relationship. An early prospective study trying to establish whether ectopically produced ANP could contribute to hyponatremia through natriuresis failed to show a correlation between plasma ANP levels and levels of plasma renin, angiotensin II, and aldosterone. The authors concluded that ANP was unlikely to contribute to hyponatremia via suppression of the renin-angiotensin II-aldosterone axis¹. In this study, there were 14 patients with elevated levels of ANP but only three had small cell carcinoma associated with hyponatremia. It is not clear why no correlation was found, however, the same group later published a study where four patients with SCLC and elevated ANP levels had inappropriately low levels of aldosterone⁹. In this second study, the patients had persistent natriuresis and low serum aldosterone despite decreasing serum sodium levels while being treated with a fluid- and sodium-restricted diet. Thus, the normal physiological aldosterone response failed to occur in patients with elevated ANP⁹. From this study, the authors were able to make three major conclusions: (i) hyponatremia in SCLC patients is often associated with inappropriate elevations of ANP instead of elevations in AVP; (ii) SCLC patients with elevated level of ANP do not seem to respond to fluid restriction, and in fact, fluid restriction may worsen the hyponatremia; and (iii) ANP appears to mediate some of its natriuretic effects through suppression of aldosterone. Interestingly, the patient presented in this manuscript displayed a disease process which exactly fits this description: elevated levels of ANP without elevated levels of ADH,

a worsening hyponatremia despite strict fluid and sodium restriction, and inappropriately low levels of aldosterone.

Hyponatremia potentially caused by SIANP should not be expected to respond to the traditional treatments used for SIADH. As discussed above, water restriction, beneficial in SIADH, may worsen the hyponatremia of SIANP if sodium intake is not increased concurrently. Likewise, if ADH levels are already suppressed in SIANP, ADH antagonists such as demeclocycline or conivaptan will have no benefits. To date, no ANP antagonists have been developed and there is no specific treatment for SIANP except for addressing the underlying cause. However, it is still important to distinguish between SIANP and SIADH. Certainly, any patient presenting with hyponatremia from SCLC should initially be placed on fluid and sodium restriction because SIADH seems to be more common. However, if the hyponatremia continues to worsen after 48–96 hours, alternative etiologies including ectopic ANP production should be considered and plasma levels of ANP and AVP should be measured to confirm the underlying etiology of the hyponatremia. It is very important to note that in the current case, the spontaneous correction of hyponatremia starting on hospital day 12 was temporally associated with appropriate tumor response to radiation therapy and, perhaps, an associated reduction in circulating levels of ectopic

ANP. This suggests that for the time being, in the cases of SIANP, early treatment of the underlying malignancy might be the best way to correct the underlying hyponatremia.

Author contributions

SEM admitted the patient, challenged the original diagnosis of SIADH, and made the diagnosis of SIANP. SEM made all the figures and wrote the manuscript. DIK and DK were the Attending Physicians on service for the care of this patient. DIK and DK helped design [Figure 3](#). All authors read and approved the final content of the manuscript.

Competing interests

No competing interests were disclosed.

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This paper reports a patient with small cell cancer and recurrent episodes of hyponatremia. The first episode was entirely consistent with SIADH and responded to water restriction and demeclocycline. The second episode of hyponatremia occurred with a nadir Na of 118 and an “inappropriately” concentrated urine of 563 and a high urine Na of 128 mm/l. The measured ADH level was low and his aldosterone level was also low. The patient seemed to be euvolemic on exam.

Clearly this patient had inappropriate urine concentration with a high urine osmolality, clinical euvolemia, and a urine Na of 128. The question is why. The single serum ADH level was low but is it correct? If it is truly low (and a level of 1.7 may still be too high for a plasma Na of 125) then something else is driving urine concentration.

My understanding of ANP is in agreement with the author’s figure 3: it increases renal blood flow, GFR, and causes natriuresis. But it does not directly generate a concentrated urine. If ANP causes too much natriuresis (ie an “inappropriate ANP” syndrome) then the urine will become concentrated as a result of ECF volume contraction and high ADH levels. If the authors are proposing that “inappropriate ANP” syndrome can generate hyponatremia independent of elevated ADH levels this would be a new physiologic principal and I need a lot more evidence that this can occur than what is presented in this manuscript.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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The Case Report is extremely well written but, unfortunately, I feel that the basic premise of the paper is fundamentally flawed. The authors argue that their patient with SCLC and hyponatremia did not have SIADH because plasma ADH levels were not elevated. Since ANP levels were high, the authors propose that ectopic secretion of ANP was the cause of hyponatremia. There are several problems with their argument. First, unless done in a research laboratory, plasma ADH levels are extremely unreliable and are not recommended. Second, even if they were measured correctly, ADH levels do not have to be "high" to be abnormal in patients with hyponatremia; they merely have to be measurable, because ADH should be unmeasurable if the serum sodium is less than 135. Third, even if ectopic ANP were the primary cause of hyponatremia, ADH levels would still be expected to be elevated secondarily because hypovolemia resulting from ANP-induced sodium wasting should stimulate ADH secretion from the posterior pituitary; i.e. ADH is inappropriately high, but not ectopically secreted. Finally, like ADH levels, the finding of elevated ANP levels does not prove ectopic secretion (though the authors are correct that ectopic secretion of ANP is common in SCLC). ANP is secondarily high in all causes of SIADH, because water retention expands plasma volume which results in ANP secretion and secondary natriuresis. The fact that their patient was clinically euvolemic is more consistent with secondary secretion of ANP in response to water retention from SIADH. If the primary problem were ectopic ANP and inappropriate natriuresis, the patient should have looked hypovolemic. The fact that their patient failed to respond to demeclocycline is not definitive – some patients may not respond to maximum doses; furthermore, response to the drug would not distinguish between SIADH and secondary secretion of ADH due to ANP-induced hypovolemia. The paper would have been more interesting if the authors had arranged for measurement of vasopressin levels in a research laboratory and if they had treated their patient with V2-receptor antagonist. There are reported cases of hyponatremia with low levels of ADH, raising the possibility that some tumors secrete a substance that is not detected immunologically as ADH, but which acts as an antidiuretic hormone. The high U_{osm} is evidence that their patient was secreting an antidiuretic hormone – they might not have been able to measure it because of problems with their assay or because their patient was secreting an antidiuretic hormone immunologically distinct from vasopressin; unfortunately we can't tell which is true.

In addition to the fundamental flaw that I see in the authors' argument, they make some statements that I don't agree with. For example, they say that water restriction would worsen hyponatremia caused by primary sodium loss. Regardless of the underlying causes, the serum sodium falls because net water intake exceeds net water loss. All else being equal, restriction of water intake always makes the serum sodium go up. If the patient is hypovolemic, the serum sodium concentration will rise with water restriction but hypovolemia will worsen.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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