Early Diagnosis of Ectopic Arginine Vasopressin Secretion

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We describe a patient who presented with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) 2 months before clinical evidence of bronchogenic malignancy. Because of the potential for the ectopic production of atrial natriuretic peptide (ANP) to mimic SIADH, both hormones were measured in this hyponatremic patient to seek a possible marker of tumor activity. A hypertonic saline infusion at presentation revealed excessive osmotically decoupled secretion of arginine vasopressin but a normal ANP response.

The acronym SIADH, for the syndrome of inappropriate antidiuretic hormone secretion, was first used to describe two patients with bronchogenic carcinoma (1), although dilutional hyponatremia associated with bronchogenic malignancy had been observed much earlier (2). Malignancy-associated SIADH is most commonly seen in patients with small-cell carcinoma of the lung and sometimes precedes clinical presentation (3). The reported frequency of SIADH in patients with this tumor is 11% (4). The implication is that the tumor itself is the origin of arginine vasopressin (AVP), which is not under osmotic control; hypothalamic control of posterior pituitary AVP release is maintained, albeit suppressed because of the hypovolemia.

Small-cell carcinoma of the lung carries a poor prognosis (mean survival 3 months without treatment). Early diagnosis is desirable, because the tumor is often highly responsive to treatment, in particular to chemotherapy. We describe a patient presenting with SIADH without evidence of malignancy. Hypertonic saline infusions with serial measurements of AVP and atrial natriuretic peptide (ANP) proved to be an early diagnostic indicator of an occult small-cell carcinoma.

Case Report

A 68-year-old man was admitted from the emergency room complaining of vague central abdominal pain and constipation. He had a previous psychiatric history and had been diagnosed as having a sociopathic personality disorder.

On examination the patient was confused, with slight tenderness in the left flank but no evidence of constipation. Blood pressure was 130/85 mmHg in supine position; pulse was 85/min and regular. The jugular venous pressure was not increased and there was no evidence of either dehydration or edema. Serum electrolyte concentrations were as follows: sodium 116 mmol/L, potassium 3.0 mmol/L, chloride 86 mmol/L, urea 2.1 mmol/L, and creatinine 104 μmol/L. The urine was not maximally dilute, with a sodium concentration of 28 mmol/L. Assessment of thyroid and adrenal function was normal with a total thyroxine concentration of 114 mmol/L and a random cortisol concentration of 887 nmol/L. The liver function tests and bone enzymes were normal at admission, and the chest roentgenogram was unremarkable, without evidence of malignancy.

In the absence of other causes of hyponatremia, with a less than maximally dilute urine and without evidence of renal, adrenal, or thyroid disease, SIADH was suspected. The patient’s serum sodium concentration responded initially to fluid restriction, rising from an initial value of 116 mmol/L to 128 mmol/L over 3 days.

To study the pathogenesis of the hyponatremia, we administered a hypertonic saline infusion of 500 mL of 50 mg/L NaCl over 104 min at a rate of 0.06 mL·kg⁻¹·min⁻¹. Blood samples were collected at 30-min intervals and at completion for measurements of plasma AVP and ANP and serum sodium and osmolality.

Plasma AVP and ANP were measured by sensitive radioimmunoassays (5, 6) by a common extraction protocol with Sep-Pak C₁₈ columns (Millipore, Watford, UK). The values obtained for these measurements are shown in Table 1, and the response of AVP to the osmotic challenge is plotted in Figure 1. The results show an increase in sodium and osmolality, consistent with a hypertonic saline infusion; the AVP results, which should, under normal osmotic control, be totally suppressed at the serum osmolality observed, show a fixed above-normal concentration. ANP concentration increased during the infusion, with a slight decrease toward the end. These results were interpreted as being consistent with an ectopic source of AVP with a normal ANP response.

A roentgenogram taken 2 months after admission showed hilar lymphadenopathy. Abdominal and thoracic computed tomography scan confirmed the likelihood of bronchial carcinoma with hepatic metastases; both adrenals appeared normal. The serum alkaline phosphatase was increased at 345 U/L and ALT was
Table 1. Changes in Plasma Analytes in Response to Infusion of 500 mL of 5 mg/L NaCl

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Na, mmol/L</th>
<th>Osmolarity, mOsmol/kg</th>
<th>AVP, ng/L</th>
<th>ANP, pg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>113</td>
<td>238</td>
<td>13.88</td>
<td>63.6</td>
</tr>
<tr>
<td>30</td>
<td>118</td>
<td>246</td>
<td>11.66</td>
<td>70.3</td>
</tr>
<tr>
<td>60</td>
<td>121</td>
<td>249</td>
<td>12.90</td>
<td>89.2</td>
</tr>
<tr>
<td>90</td>
<td>121</td>
<td>254</td>
<td>13.48</td>
<td>157.8</td>
</tr>
<tr>
<td>120</td>
<td>124</td>
<td>257</td>
<td>12.66</td>
<td>116.1</td>
</tr>
</tbody>
</table>

Fig. 1. Relation between plasma AVP and osmolality during hypertonic saline infusion
The area between the solid lines represents the range of values seen in normal subjects; the horizontal line indicates the detection limit of the assay.

increased at 91 U/L, providing biochemical support of the computed tomography findings. A lymph node biopsy revealed infiltration by metastatic small-cell carcinoma. Unfortunately, the patient’s condition deteriorated and he died 4 months after initial presentation. An autopsy confirmed the presence of small-cell carcinoma within the right lower lobe bronchus with metastatic tumor in the hilar lymph nodes and liver. Brain and adrenals were free of infiltration.

Discussion

One explanation of the steady-state fluid balance and natriuresis observed in patients with SIADH is an increased production of ANP (7). There is a wide individual variation in plasma concentrations of ANP under basal conditions in SIADH, but a concentration of 63.6 ng/L would not be considered significantly increased even in a normal 68-year-old man. Of interest is the normal qualitative response of ANP during the infusion, suggesting that the initial degree of intravascular volume expansion was relatively mild in relation to the hyponatremia and that physiological control of ANP remained intact and unaffected by significant and persistent AVP concentrations. Thus, AVP does not appear to influence the physiological control of ANP directly but only through its effect on volume expansion through water retention (8).

SIADH, in association with both malignancy and nonmalignant conditions, has been classified into four categories (9). In type A, there is an erratic, osmotically decoupled, high secretion of AVP; type B is characterized by a reset osmostat with the normal release of AVP but at a lower osmotic setting; in type C, there is an osmotically nonsuppressible low secretion or leak of AVP but with the retention of osmotic control at physiological osmolality; and in type D, osmotic control is apparently normal. These categories need not be mutually exclusive in malignancy SIADH, however, because the difference between types A, C, and D can be explained by different concentrations of hormone production by the tumor and the relative renal responsiveness of the kidney to AVP. In addition, a reset osmostat (type B) may result from established chronic dilutional hyponatremia associated with low AVP production.

An alternative explanation of apparent normal osmotic control of AVP (type D) or of reset osmostat (type B) may be the production by the tumor of a separate hormone that acts on water and salt metabolism. The potential of ectopic ANP secretion to mimic SIADH is of interest, a case describing ectopic ANP production having recently been described (10). Indirect evidence also exists to support such a presentation. One case of malignant infiltration of the atria with squamous-cell carcinoma of the bronchus resulted in a gross increase of plasma ANP, presumed to be of atrial origin, and a presentation that included a plasma and urine electrolyte pattern consistent with SIADH (11). In a separate study, autopsy examination of cell lines from small-cell carcinomas from five patients who had all had SIADH revealed that two had expression of AVP mRNA but three had expression of ANP mRNA (12).

Our patient revealed an erratically high and osmotically decoupled secretion of AVP. The ANP response was normal with a doubling of its concentration during hypertonic saline infusion. Monitoring of both AVP and ANP in cases of unexplained SIADH may reveal early evidence of malignancy and may indicate a useful marker of tumor activity—AVP or ANP—during active treatment.

References


