Inappropriate Antidiuretic Hormone Secretion in Carcinoma of the Lung*

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Four cases with inappropriate antidiuretic hormone syndrome associated with carcinoma of the lung are reported. It is concluded that certain tumors manifest a capability to synthesize and release a substance similar to antidiuretic hormone which enhances water reabsorption, leading to dilution and expansion of the extracellular fluid volume. These changes in the extracellular fluid volume stimulate the third factor mechanism which depresses proximal tubular sodium reabsorption, resulting in a continued renal salt loss despite the existing hyponatremia. The simple restriction of fluid intake to 500-750 ml per day along with an adequate intake of sodium will result in correction of the hyponatremia and relief of the distressing symptoms. Permanent cure is possible when complete removal of the tumor is technically feasible.

It has been known for many years that certain carcinomas can produce many varied systemic manifestations in the absence of metastases. One of the most interesting groups of manifestations has been that resulting from excessive water retention and renal salt loss due to inappropriate secretion of antidiuretic hormone (ADH). This is generally known as the inappropriate antidiuretic hormone syndrome (IADHS) and was first recognized in patients with bronchogenic carcinoma.¹

Before our general discussion, we wish to present four cases with inappropriate antidiuretic hormone syndrome associated with carcinoma of the lung. The significant clinical and laboratory findings are shown in Figure 1 and Table 1.

CASE 1:
A 71-year-old white man was admitted to the hospital with a five-month history of substernal and epigastric pain. One week prior to admission, he developed anorexia, lethargy, mental confusion and weakness. Past history revealed he had smoked more than 20 cigarettes daily for the greater part of his life.

On physical examination, he was debilitated and appeared mentally confused, dull, and lethargic. The liver was enlarged, nodular, and tender. Chest roentgenogram showed an infiltrative density near the right cardiac border with pleural reaction near the cardiophrenic angle. A needle biopsy of the liver revealed metastatic anaplastic carcinoma. Due to the low serum sodium, large quantities of sodium were given both intravenously and orally with only a temporary improvement in the sodium level. Total fluid intake was then limited to 500 ml daily, and rapid correction of the hyponatremia and improvement in the patient's mental status occurred. There was a gradual deterioration in his condition, and he expired six months from the onset of symptoms.

Post-mortem examination showed undifferentiated bronchogenic carcinoma of the small-cell type with metastases to regional nodes, liver, bone, and pituitary. (The pituitary metastasis had completely replaced the posterior lobe.)

CASE 2:
A 70-year-old white man was admitted to the hospital with complaints of chest pain and dyspnea of one day's duration. Past history revealed that he had chronic lymphocytic leukemia and had been treated with chlorambucil (Leukeran). The last treatment was three months prior to this admission.

Physical examination revealed a dull, confused, and lethargic man with a normal blood pressure, skin turgor, and no edema.

There was a large density seen in the left hilum on the chest x-ray film. Red blood cell volume determination using Cr⁵¹ showed a decrease in red blood cell volume and a slight increase in plasma. Bronchoscopy revealed a lesion in the left primary bronchus, and bronchial washings from this area were found to contain poorly differentiated malignant cells.

Due to the poor cardiovascular status, the treatment consisted of supervoltage radiation to the tumor and a restriction of oral fluids to 750 ml daily. With this restriction, there was a prompt rise in serum sodium and improvement in his mental status. After completion of radiation treatment (6173 r in 33 days), he was allowed a liberal fluid intake (2000-3000 ml/24 hr). His serum sodium decreased from normal to 125 mEq/L within three days.

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Table 1—Significant Laboratory Features in Four Patients with Bronchogenic Carcinoma and Associated Inappropriate Antidiuretic Hormone Secretion

<table>
<thead>
<tr>
<th>Case</th>
<th>BUN (mg%)</th>
<th>Serum Electrolytes (mEq/L)</th>
<th>Urine Electrolytes (mEq/L)</th>
<th>Urine Specific Gravity</th>
<th>Serum Osmolality (mOsm/L)</th>
<th>Urine Osmolality (mOsm/L)</th>
<th>Urine 17-Hydroxy (mg/24 hrs.)</th>
<th>Plasma Steroids (mg/24 hrs.)</th>
<th>Plasma Corticoids (mg/24 hrs.)</th>
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<tr>
<td>1</td>
<td>9</td>
<td>111 4.5 66 27</td>
<td>1.025</td>
<td>104 63 46</td>
<td>93 60 46</td>
<td>1019 964 743</td>
<td>16 12 5</td>
<td>10 10 10</td>
<td>285-305 600-1000 5-16 12-24 5-20</td>
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<td>2</td>
<td>13</td>
<td>110 5 80 22</td>
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<td>106 60 48</td>
<td>92 60 46</td>
<td>1008 958 743</td>
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<td>3</td>
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<td>107 4.6 72 23</td>
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<td>4</td>
<td>13</td>
<td>127 5.3 89 27.5</td>
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<td>105 60 48</td>
<td>92 60 46</td>
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<td>15 12 5</td>
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<td>250-275 600-1000 5-16 12-24 5-20</td>
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<tr>
<td>Normal</td>
<td>285-305</td>
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His subsequent course was gradually downhill, and he expired four months following the onset of symptoms.

Post-mortem examination showed oat-cell bronchogenic carcinoma with metastases to the periaortic lymph nodes, liver, right adrenal, and bone.

Case 3:

A 61-year-old white man was admitted to the hospital with complaints of anorexia, nausea, vomiting, and weakness of one month's duration. He had lost 15 lb in weight during this period. His past history revealed that he had smoked 20 cigarettes and five cigars daily for many years.

Except for slight confusion and a few rales located over the right upper chest, the physical examination was not remarkable.

Chest roentgenograms showed partial atelectasis of the right upper lobe. Bronchoscopy demonstrated markedly constricted right upper lobe bronchi occluded by thick purulent secretions. There was evidence of extrinsic pressure on the membranous portion of the right intermediate bronchus. Cytologic tests of bronchial washings were negative for malignant cells.

While in the hospital, he was notably confused, lethargic, and sometimes disoriented. On several occasions, he experienced Jacksonian seizures. On a diet with adequate sodium and fluids restricted to 1000 ml daily, his serum sodium rose to normal, and clearing of his sensorium and cessation of seizures resulted. On the basis of the chest roentgenogram and clinical and laboratory findings, supplementary radiation treatment to the tumor and adjacent mediastinum was begun. Radiation treatment had to be discontinued after 16 days following a tumor dose of 3240 r due to the poor general condition of the patient. His condition continued to deteriorate, and he expired two months following the onset of symptoms.

Post-mortem examination showed small-cell bronchogenic carcinoma which had metastasized to bone, liver, pancreas, adrenal, and lymph nodes.

Comment: There was laboratory evidence (elevated urine and plasma 17 hydroxycorticoids) to suggest that the tumor was secreting ACTH as well as ADH. The cortical layers of the adrenals at necropsy were thickened, suggesting increased activity; however, assays of the tumor tissue failed to demonstrate ACTH activity. Multiple hormone secretion by single tumors is well established. Our experience with five patients with ACTH-producing bronchogenic carcinoma was recently reported.

Case 4:

A 57-year-old white man was admitted to the hospital with a one-week history of right chest pain, increasing dyspnea, and a ten-pound weight loss. Past history revealed that he had smoked approximately 20 cigarettes daily for over 30 years.

Physical examination revealed absence of breath sounds over the right hemithorax with flatness to percussion. The liver extended two fingers below the right costal margin, with a non-tender smooth anterior edge.

Chest roentgenograms showed complete opacification of the right hemithorax with a shift in the heart and mediastinal structures to the opposite side. Bronchoscopy was normal, but cytologic studies of bronchial washings showed malignant cells. Blood volume determinations using radioactive iodine showed the plasma volume increased above the normal range. Cytologic studies revealed malignant cells in the pleural fluid.

On the basis of the chest roentgenogram, positive pleural cytology, and clinical and laboratory findings, he was treated with the drug cyclophosphamide (Cytoxan), 1800 mg, and a regular diet. His fluid intake was restricted to 750 ml daily, with a return of the serum sodium to normal. The patient's course was progressively downhill, and death occurred in 34 days from the onset of symptoms.

Post-mortem examination showed adenocarcinoma (Fig 2) of the right lung with metastases to the left lung, lymph nodes, liver, adrenals, and bone. There was a large pulmonary embolus found in the left lung.

FIGURE 1. Clinical response as measured by serum sodium levels to increase sodium intake and fluid restriction in patients with inappropriate antidiuretic hormone syndrome.
CARCINOMA OF THE LUNG

In recent years, it has been recognized that certain non-endocrine tumors synthesize and release hormones or hormone-like substances, resulting in various endocrinopathies. The ability of these tumor cells to synthesize and release complex polypeptides, which their parent cells are unable to do, seems rather surprising at first. Heretofore, tumor cells have usually been characterized by loss of specialized function, particularly with the undifferentiated carcinomas. Does the formation of these hormones really represent increased differentiation of these tumor cells rather than the usual dedifferentiation? It probably does not, since all cells, especially normal cells, contain identical chromosomes with the genetic information already present for synthesizing hormones. In normal non-endocrine cells, the functions of these genes are suppressed by specific controls, and it is the loss of these suppressive controls that allows non-endocrine cells to produce specific hormones. Thus, these syndromes are probably another manifestation of tumor cell de-differentiation. This may explain why many of these endocrine syndromes occur with undifferentiated tumors more often than with differentiated tumors. This is particularly true of the inappropriate antidiuretic hormone syndrome, which occurs predominantly in patients with undifferentiated or oat cell bronchogenic carcinoma. However, more differentiated tumors, as well as non-neoplastic diseases, may produce the same syndrome, as shown in Table 2. This paper will be limited to a discussion of inappropriate antidiuretic hormone syndrome associated with bronchogenic carcinoma.

The first evidence to suggest that the hypotremia associated with undifferentiated bronchogenic carcinoma is due to excessive antidiuretic hormone was the observation that the urine osmolality was consistently greater than that of the plasma in the presence of normal or over-hydration and a normal glomerular filtration rate. ADH is the only known substance capable of producing renal tubular water reabsorption against an osmotic gradient. In the absence of ADH, the urine osmolality will approach that of the plasma. Since the normal response to low plasma osmolality is a depression of ADH secretion, the presence of elevated levels of ADH in these patients is "inappropriate." A decrease in blood volume stimulates release of ADH, but in this syndrome, blood volume determinations have been found either normal or increased.

These conclusions were substantiated by Leaf et al. who were able to construct an experimental

Table 2—Disorders Producing Inappropriate Antidiuretic Hormone Syndrome

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<td>E. Idiopathic</td>
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model which completely mimicked the inappropriate antidiuretic hormone syndrome. This was done by injecting vasopressin tannate (Pitressin tannate) in oil daily to normal subjects given free access to water. These subjects retained water, developed dilutional hyponatremia, and continued to excrete sodium in the urine despite the presence of hyponatremia. In addition, the urine osmolality exceeded that of the plasma.

Subsequent studies by Bower, et al., using bioassay techniques, confirmed the presence of an increase in antidiuretic activity in the plasma of patients with bronchogenic carcinoma with inappropriate antidiuretic hormone syndrome.

The weight of indirect evidence suggests that the material from the tumor itself, rather than ADH released inappropriately from the posterior pituitary, is responsible for IADHS, since attempts to block antidiuresis in patients with bronchogenic carcinoma with alcohol have been unsuccessful. It is also noteworthy that the posterior pituitary gland tissue need not he present for the syndrome to occur in association with release of ADH by the tumor.

These indirect studies have been substantiated by the demonstration of large quantities of antidiuretic material by assay of tumor tissue in 12 cases. Thus, there appears to be little doubt that the IADHS, when occurring in association with bronchogenic carcinoma, is due to production and release of ADH by the tumor itself in an inappropriate fashion. Therefore, the hypo-osmolality with corresponding hyponatremia and the increased blood volume has no inhibitory effect on the release of ADH by the tumor.

The presenting complaints fell into two groups—those due to the primary lung cancer, and those due to the hyponatremia with corresponding hypo-osmolality (Table 3). Those symptoms relating to the hypo-osmolality of the body fluids can usually be correlated with the degree of hyponatremia. In patients with serum sodium at levels of 120 mEq/L or more, there may be no complaints. Generally, however, when the serum sodium falls below 120 mEq/L, a number of symptoms appear. Since these symptoms are due to the hypotonicity of the body fluids, the symptom complex is that of water intoxication manifested by anorexia, nausea, vomiting, increased irritability, and confusion. With the serum sodium below 110 mEq/L, neurologic abnormalities appear, characterized by decrease or loss of reflexes, muscular weakness, bulbar or pseudobulbar palsy, stupor, and convulsive seizures. These symptoms may frequently mimic cerebral metastases. It is at this stage that hyponatremia seems to be of some importance. This probably explains the lack of correlation between the symptoms and the degree of hyponatremia in some rare cases.

In some patients, hyponatremia may not be evident unless sufficient water load is available. In patients with bronchogenic carcinoma who are suspected of having IADHS, a challenging water load of 4 liters followed by serum sodium evaluation the following day may reveal unsuspected cases.

<table>
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<th>Table 3—Symptoms and Signs</th>
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<td>Due to Tumor</td>
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<tr>
<td>1. Cough</td>
</tr>
<tr>
<td>2. Chest Pain</td>
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<td>3. Dyspnea</td>
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<tr>
<td>5. Weight Loss</td>
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<td>6. Weakness</td>
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Table 4—Differential Diagnosis Inappropriate Antidiuretic Hormone Syndrome

1. Psychogenic polydipsia
2. Addison's disease with IADHS
3. Hypopituitarism (IADHS present?)
4. Postoperative state
5. Sodium loss with water replacement
6. Congestive heart failure
7. Carbons, liver

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nosis clear. The second exception is excessive water retention, which is generally accepted, there is considerable controversy over the mechanism responsible for the continued loss of sodium in the urine. This loss by the kidney in the presence of a hyponatremia has been attributed by various authors to one of three factors: (1) increase in glomerular filtration rate, (2) decrease in aldosterone secretion, and (3) "third factor" effect. However, most studies have indicated that the first two factors are of little significance; that is, glomerular filtration rate has not been increased nor aldosterone secretion decreased. It has been established that a rise in the filtered load of sodium is not required in order for salt loss to occur, as in steroid-treated normal subjects in whom extracellular fluid volume is expanded by administration of vasopressin and water. This steroid administration showed also that a decrease in aldosterone secretion, or factor 2, is not required for a urinary loss of sodium to occur. Thus, it appears that the third factor plays a critical role in mediating the natriuretic response during expansion of the extracellular fluid volume found in IADHS.

The recent observation that a third factor is involved in the control of sodium excretion and of the extracellular fluid volume opens a new and exciting chapter in renal physiology. The third factor is so named because it is independent of the two other factors long believed to be the exclusive determinants of sodium excretion.

This factor appears to be important in the volume control system at the level of the nephron, and it serves to reset glomerulotubular balance. This is to say that in a steady state condition, a constant fraction of the filtered sodium is reabsorbed in the proximal tubule despite variations in the glomerular filtration rate. Thus, there is a constant proportionality between glomerular filtration rate (filtered Na load) and proximal tubular reabsorption of sodium for any fixed volume of extracellular fluid. This proportionality prevents large changes in sodium excretion with spontaneous fluctuations in glomerular filtration rate, but does not implement the maintenance of external sodium balance in presence of a changing rate in salt intake. Therefore, with extracellular fluid volume expansion and increased glomerular filtration, the fraction of filtered load of Na⁺ reabsorbed in the proximal tubule decreases, and with extracellular cellular fluid volume depletion and decreasing glomerular filtered sodium load, the fraction of sodium reabsorbed in the proximal tubule is increased. The third factor does not disrupt the glomerulotubular balance, but rather resets it in the direction required for the preservation of sodium balance.

The most impressive evidence that the third factor is a hormonal substance has been presented by Martinez-Maldonado et al. who showed that the plasma from saline-loaded dogs and rats contained a substance that inhibited proximal tubular sodium reabsorption in recipient rats. The third factor appears, therefore, to be a hormone whose release is related to some function of the extracellular fluid volume. Its site of synthesis still remains a mystery. It is interesting, however, that the third factor actually is ablated in saline-loaded animals when the thoracic inferior vena cava is constricted, but is not affected by constriction of the abdominal inferior vena cava, aorta, or the renal arteries.

The treatment of this syndrome should be directed toward: (1) the correction of the hyponatremia and (2) resection of the underlying bronchogenic carcinoma.

The simple restriction of fluid intake to within a range of 500-750 ml per 24 hours with allowances for adequate sodium intake will usually correct the hyponatremia and thus alleviate the severe symptoms. In acute emergencies with very low serum sodium and severe neurologic symptoms, the initial use of pharmacologic doses of salt-retaining steroid and hypertonic salt solution may be indicated.

Surgical resection of the bronchogenic carcinoma has led to prompt correction of the syndrome if the tumor is completely removed. Treatment using other modalities, such as supervoltage radiation and cyclophosphamide (Cytoxan), did not diminish the severity of the syndrome in our patients.

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REFERENCES


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