Severe Hyponatremia Due to Inappropriate Secretion of Antidiuretic Hormone following Pleurodesis

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Abstract

A 69-year-old man was diagnosed as having syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (serum sodium: 113 mEq/L) 13 days after a right upper lobectomy due to squamous cell carcinoma of the lung (pT1N0M0, stage IA) whereas the preoperative serum sodium level was nearly normal. He had undergone pleurodesis by instillation of OK432 at 2 and 5 days after surgery for prolonged air leakage. Since other possible causes of SIADH, such as residue of lung cancer, pulmonary infections, brain disorders, or known causative drugs were ruled out, the SIADH in this patient was likely associated with pleurodesis by the use of OK-432. A review of similar cases reported suggests that it is important to be aware of the possibility of severe hyponatremia due to SIADH after chemical pleurodesis.

Key words: OK-432, thoracotomy, pleuritis, lung cancer, pleurodesis

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Introduction

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is the most frequent cause of hyponatremia. The causes of SIADH can be categorized as related malignant diseases, pulmonary diseases, disorders of the central nervous system, drugs, and others (1). We describe a rare case of SIADH associated with pleurodesis by OK-432.

Case Report

A 69-year-old man was admitted to the hospital because of severe nausea and malaise. The patient, a former smoker, had been healthy until he underwent a right upper lobectomy due to squamous cell carcinoma of the lung (pT1N0M0, stage IA) under video-assisted thoracoscopy at another hospital 13 days before the admission. Post-operative course was uneventful except for prolonged pleural air leakage which was treated by instillation of a sclerosing agent [OK-432, 5 klinische einheiten (KE)] in the right pleural cavity at 2 and 5 days after the operation. He was discharged on the 10th postoperative day. On physical examination, the patient was alert, his body temperature was 36.5°C, pulse was 90/min, respiration rate was 16/min, and blood pressure was 163/101 mmHg. The lungs, heart and abdomen were normal. No edema was found in the extremities. Neurological examinations revealed no abnormalities. Laboratory examinations showed severe hyponatremia (113 mEq/L) with decreased serum osmolarity (231mosm/L) and increased urine osmolarity (479 mosm/L). The serum levels of sodium at the preoperative evaluation and 7th postoperative day were 134 mEq/L and 130 mEq/L, respectively (Fig. 1). The excretion of sodium into the urine was 130 mEq/L. Serum anti-diuretic hormone (ADH) level was elevated to 5.5 pg/mL (normal 0.3-3.5 pg/mL) despite severe hyponatremia, while thyroid and adrenal functions were normal. Other laboratory examinations, including a blood cell count, urinalysis, liver and renal function tests and plasma glucose level, showed normal values. The diagnosis of SIADH was made based on these laboratory findings. The radiological examinations including a chest X-ray, computed tomography of the chest and abdomen and brain magnetic resonance imaging were normal except for postoperative changes in the right thoracic cavity with a small amount of effusion. He was not given any drugs that are known to enhance the action or release of ADH. There were no significant changes in hemodynamics or fluid balance and no infection in the protein.
central nervous system or respiratory tract during the previous hospitalization. Preoperative evaluation including a positron emission tomography (PET) scan showed that a malignant lesion was limited to the right upper lobe of the lung. He was treated with infusion of hypertonic saline (2% NaCl) and fluid restriction (600 mL/day). His serum sodium and ADH levels returned to nearly normal ranges within 2 weeks and he was discharged. Hyponatremia did not recur 3 months after the discharge without fluid restriction.

**Discussion**

OK-432, a lyophilized preparation of an attenuated *Streptococcus pyogenes*, is commonly used as a sclerosing agent for pleurodesis in patients with pleuritis carcinomatosa, recurrent pneumothorax and prolonged air leakage after thoracotomy (2). We consider that SIADH in the present case was related to pleuritis caused by the instillation of OK-432 or a direct influence of OK-432, since other possible causes such as malignant diseases, central nervous system disorders, or pulmonary infections were ruled out by preoperative evaluation and examinations upon admission. Although transient increases in ADH secretion induced by surgical stress have been reported, they rarely cause hyponatremia following surgery, and these changes usually occur within 24 hours after surgery and return to normal levels within several days (3, 4). Furthermore, as reported in other cases of SIADH or syndrome of inappropriate diuresis (SIAD) associated with pleuritis, the hyponatremia improved and serum ADH returned to normal level as pleuritis recovered during a three-month follow-up (1, 5, 6). Therefore SIAD(H) is likely associated with pleuritis caused by instillation of OK 432 or OK432 per se. Among the myriad of causes of SIADH, pleuritis or other pleural disease is rare. There have been several cases of SIADH associated with pleural tumor, empyema or pleuritis, but SIAD(H) related to pleurodesis is very rare (5-8). There have been three cases of severe SIAD-(H) associated with pleurodesis including the present case (Table 1) (5, 6). All patients underwent pleurodesis after thoracotomy. The symptoms occurred 9-13 days after instillation of sclerosing agents [2 cases; OK-432, and 1 case; cis-dichlorodiammine platinum (CDDP)]. Serum ADH was elevated in two cases. There are several possible reasons for inappropriate release of ADH in patients with pleurodesis. Abnormal stimulation of arterial and atrial baroreceptors or cardiopulmonary mechanoreceptor by hemodynamic changes, stress, hypoxia and pain during the procedures of pleurodesis may possibly induce the release of ADH through the hypothalamo-hypophyseal system (1, 9). However these mechanisms explain neither the occurrence of this syndrome

**Figure 1.** The clinical course, showing a significant decrease in serum sodium levels 12 days after instillation of OK-432. Serum sodium (open circle) gradually increased after sodium supplementation and fluid restriction. Decrease in serum C-reactive protein (closed circle) was observed 3 to 4 weeks after pleurodesis.

**Table 1.** List of Cases of SIADH Associated with Pleurodesis

<table>
<thead>
<tr>
<th>case</th>
<th>age</th>
<th>sex</th>
<th>primary disease</th>
<th>drug for pleurodesis</th>
<th>symptoms</th>
<th>onset of symptoms after instillation</th>
<th>serum sodium (mEq/L)</th>
<th>serum ADH (pg/mL)</th>
<th>literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>M</td>
<td>thymoma</td>
<td>CDDP*</td>
<td>LOC**</td>
<td>9 days</td>
<td>104</td>
<td>0.6</td>
<td>(5)</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>M</td>
<td>lung metastasis</td>
<td>OK432</td>
<td>LOC</td>
<td>9 days</td>
<td>106</td>
<td>16.2#</td>
<td>(6)</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>W</td>
<td>lung cancer</td>
<td>OK432</td>
<td>anorexia</td>
<td>13 days</td>
<td>113</td>
<td>5.9#</td>
<td>present case</td>
</tr>
</tbody>
</table>

*CDDP/cis-dichlorodiammine platinum, **LOC: loss of consciousness, # exceeded normal values (0.3-3.5 pg/mL)
nor the delay of hyponatremia 13 days after the procedures in this case, because the postoperative course was uneventful except for prolonged air leakage. An alternative hypothesis is that the inflammation in the lung or pleural cavity may cause an abnormal stimulation of vagal receptors and result in abnormal secretion of ADH from the pituitary gland (6, 9). The hypothesis is consistent with the prolongation of SIAD(H), since there have been some data suggesting that intrapleural OK-432 can induce persistent inflammatory process with elevated CRP levels up to 28 days after the procedure (10). The contribution of thoracotomy to SIADH is unclear. To our knowledge, all reported cases of SIADH associated with pleurodesis occurred after thoracotomy, whereas pleurodesis occurs much more frequently in cases of malignant pleuritis or recurrent pneumothorax unrelated to thoracic surgery.

In conclusion, it is important to be aware of the possibility of severe hyponatremia due to SIADH after pleurodesis using OK-432 or other sclerosing agents.

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References


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