CASE REPORT

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SINONASAL NEUROENDOCRINE CARCINOMA IN ASSOCIATION WITH SIADH

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Abstract: Background. Neuroendocrine carcinoma (NEC) is a rare malignancy of the nasal cavity or paranasal sinuses. The syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH) has not been previously reported in association with this cancer.

Methods. We report a 30-year-old woman with histologically confirmed neuroendocrine carcinoma who also demonstrated SIADH. After successful chemotherapy and radiotherapy treatment for the neoplasm, her SIADH resolved. A literature search found eight cases of olfactory neuroblastoma (ONB) associated with SIADH, four of which resolved after treatment of the malignancy.

Results. Treatment of the underlying malignancy resulted in the immediate resolution of the SIADH.

Conclusions. We report the first case of SIADH associated with NEC, which resolved after treatment of the cancer. A direct cause and effect between ONB/nasal NEC and SIADH has been established in previous reports.


Keywords: neuroendocrine carcinoma; sinonasal; SIADH; olfactory neuroblastoma

Olfactory neuroblastoma (ONB) has been subtyped according to both light-microscope and electron-microscope findings into two groups, depending on their small cells and the presence or absence of true rosettes and neurofibrillary material1: neuroblastomas proper and neuroendocrine carcinomas (NECs) (Table 1).

Syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH) has been associated with a considerable number of neoplastic and nonneoplastic diseases, with oat cell lung cancer being the most common. The syndrome results from excessive amounts of vasopressin produced by the tumor, which leads to hyponatremia without edema and increased sodium loss in the urine. A review of the Western literature revealed eight cases of ONB associated with SIADH. However, we found no report of the association of this syndrome with NEC. Therefore, we thought that a unique case of NEC of the nasal cavity associated with SIADH that resolved with treatment of the neoplasm was worth reporting.

CASE REPORT

On July 2, 2001, a 30-year-old white woman was seen with a 4-month history of anosmia and a neck
mass that had been present for 1 month. The patient’s husband had mentioned that she drank water frequently, which was not unusual for her. She had no medical history of note and was a non-smoker. There was no history of nausea or vomiting, and the patient denied use of any medications before presentation. Clinically, she demonstrated a fleshy mass high above the middle turbinates on both sides, with palpable adenopathy within the left neck. Three enlarged nodes were palpable in level II, the largest of which measured 2 cm. A smaller 1-cm node was palpated in level IV. Fine-needle aspiration of one of the neck nodes revealed features suggestive of either a high-grade malignant lymphoproliferative disorder or a metastatic undifferentiated neoplasm. Her pulse and blood pressure were normal, and the rest of her physical examination was unremarkable.

CT and MRI scans confirmed the nasal mass high in the nasal cavity encroaching on the cribiform plate without obvious intracranial extension (Figure 1). The lesion extended into the right nasal cavity through the nasal septum, with soft tissue thickening within the ethmoid, frontal, and sphenoid sinuses. CT examination of her chest and abdomen was normal. Her blood chemistry studies demonstrated hyponatremia, with a sodium level of 125 mEq/L (135–145 mEq/L) and a chloride level of 91 mEq/L (96–108 mEq/L). Repeat blood tests revealed a sodium level of 119 mEq/L and a serum osmolality of 240 mOsm/kg (280–300 mOsm/kg). The urine osmolality was 480 mOsm/kg (300–900 mOsm/kg), and the urinary sodium was 32 mEq/L. There were no neurologic or psychiatric symptoms, and no abnormalities were found on neurologic examination. The patient’s thyroid, adrenal, and renal function tests were normal.

The patient was diagnosed with SIADH. Water restriction was implemented, and she was given 300 mg demeclocycline three times a day. The patient discontinued this medication herself because of nausea after 3 days. On July 10, 2001, the patient underwent a biopsy of the nasal mass. The histologic findings were that of a high-grade small blue cell undifferentiated neoplasm that was diffusely and strongly positive for synaptophysin antibody and demonstrated strong perinuclear punctate staining with keratin antibody. The patient was diagnosed with small cell

**Table 1.** Histologic classification of sinonasal neuroendocrine tumors

<table>
<thead>
<tr>
<th>Neuroblastoma proper</th>
<th>Neuroendocrine carcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Without olfactory differentiation</strong></td>
<td><strong>With olfactory differentiation</strong></td>
</tr>
<tr>
<td>LM</td>
<td>Olfactory rosettes</td>
</tr>
<tr>
<td>Mitoses unusual</td>
<td>Admixture with granules</td>
</tr>
<tr>
<td>Fibrillary material found between cells</td>
<td>Neurofibrillary component not seen</td>
</tr>
<tr>
<td>Foci of necrosis and small calcific deposits seen</td>
<td>Growth pattern is solid nests without rosettes</td>
</tr>
<tr>
<td>Homer-Wright rosettes</td>
<td>Cells are larger</td>
</tr>
<tr>
<td>EM</td>
<td>Dense core granules are present in the cytoplasm and cytoplasmic extensions</td>
</tr>
<tr>
<td>Accumulation of small dense core granules within dendritic processes</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EM, electron microscopy; LM, light microscopy.

The patient was diagnosed with SIADH. Water restriction was implemented, and she was given 300 mg demeclocycline three times a day. The patient discontinued this medication herself because of nausea after 3 days. On July 10, 2001, the patient underwent a biopsy of the nasal mass. The histologic findings were that of a high-grade small blue cell undifferentiated neoplasm that was diffusely and strongly positive for synaptophysin antibody and demonstrated strong perinuclear punctate staining with keratin antibody. The patient was diagnosed with small cell
neuroendocrine carcinoma of the nasal cavity. The SIADH was attributed to this lesion (Fig 2 and 3).

After a multidisciplinary review of her case, she was treated with chemotherapy followed by radiotherapy. A neck dissection would be performed should the neck adenopathy persist after this treatment. In October 2001, the patient completed four cycles of cisplatin (60 mg/m², day 1) and etoposide (120 mg/m², days 1, 2, and 3) with a complete radiologic response of the primary tumor and a partial response of the neck node metastasis. Therefore, it was decided to proceed with radiation therapy to consolidate the treatment of the primary cancer. The patient received radiotherapy with 5940 cGy to the nasal region using twice daily treatments with similar doses administered to each side of her neck. After completion of radiation therapy on December 13, 2001, a small mass still palpable remained in level II. Thus, as it was planned, a neck dissection was performed on January 31, 2002. This consisted of a left selective neck dissection of levels II–IV with preservation of the accessory spinal

erve, sternocleidomastoid muscle, and the internal jugular vein. Histologic examination of the specimen revealed no tumor.

After completion of the first cycle of chemotherapy, her SIADH resolved, with her most recent Na level of 144 mEq/L on July 26, 2002. The patient is well with no evidence of disease at the time of this report.

DISCUSSION

SIADH or Schwartz-Bartter syndrome is an uncommon condition, which usually occurs as a paraneoplastic syndrome in association with a wide variety of cancers. In a review by Ferlito et al² in 1997, 70 cases of SIADH were found to be associated with head and neck malignancies. Other causes of SIADH include pulmonary disease, central nervous system disorders, and various drugs. ADH or its human biologically active form, arginine vasopressin (AVP), is produced within the hypothalamus and then trans-
ported to the posterior pituitary, where it is stored and released. Physiologically, ADH maintains a constant serum osmolality and intravascular volume by its action on the renal tubular system, which results in retained water and concentrated urine.

Patients with SIADH gain weight secondary to water retention and might exhibit neurologic signs because of cerebral edema. Typically, however, patients exhibit no edema or evidence of volume depletion and do not appear dehydrated. The clinical severity is dependent on the degree of hyponatremia, with lethargy, confusion, convulsions, and coma being the most serious symptoms. Other causes that might resemble SIADH, such as adrenal insufficiency, hypothyroidism, renal disease, neurologic and pulmonary disorders, and medications such as diuretic use must be excluded. Fortunately, the patient in this report had no ill effects from her SIADH other than polydipsia.

The diagnosis of SIADH is made when patients fulfill strict diagnostic criteria. These include (1) decreased plasma osmolality, <275 mOsm/kg water; (2) inappropriate urine concentration, with urine osmoles greater than 100 mOsm/kg; (3) euvolemic volume status; (4) elevated urinary sodium excretion; and (5) absence of other potential causes of increased ADH, including hypothyroidism, hypercortisolism, and recent diuretic use. This patient had demonstrated all of these criteria for a diagnosis of SIADH.

The treatment of SIADH requires removal of the underlying cause; however, symptomatic treatment involves fluid restriction or administration of demeclocycline, a tetracycline antibiotic, which can produce nephrogenic diabetes insipidus. Emergency cases might require rapid infusion of normal saline or hypertonic saline.

Squamous cell carcinoma is the most common malignancy associated with SIADH in the head and neck, accounting for 78% of cases. Only eight cases of SIADH have been reported in the Western literature that have been attributed to ONBs. We believe this is the first case of SIADH associated with a nasal neuroendocrine carcinoma. All cases of ONB with SIADH are summarized in Table 2.

Of the nine patients with SIADH associated with sinonasal neuroendocrine malignancy, four had symptoms, signs, and laboratory findings conclusive of SIADH. In three reports, patients had episodic hypertension. The mechanism for this effect is unknown; however, it is thought that the pressor effect of ADH/AVP is the most likely cause. Five cases, including the patient in this report, demonstrated complete resolution of SIADH after treatment of the neoplasm. In two cases, tumor analysis confirmed tissue AVP production. This evidence strongly suggests a cause-and-effect relationship between ONB and ADH/AVP secretion.

This report represents the first case of SIADH associated with a sinonasal NEC, which resolved after successful treatment of the malignancy with neoadjuvant chemotherapy and radiation treatment. A direct cause and effect between ONB/

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Sex</th>
<th>Presentation with SIADH</th>
<th>Blood Pressure (mmHg)</th>
<th>Plasma AVP</th>
<th>Tumor AVP/ADH Radioimmunoassay</th>
<th>Tumor AVP/ADH Immunocytochemistry</th>
<th>Histology</th>
<th>SIADH following tumor treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>30</td>
<td>F</td>
<td>No</td>
<td>Normal</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>NEC</td>
<td>Resolution</td>
<td>NED</td>
</tr>
<tr>
<td>Miura et al5</td>
<td>56</td>
<td>M</td>
<td>No</td>
<td>NS</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ONB</td>
<td>–</td>
<td>Death from metastases</td>
</tr>
<tr>
<td>Myers et al6</td>
<td>79</td>
<td>F</td>
<td>No</td>
<td>NS</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ONB</td>
<td>–</td>
<td>Death from metastases</td>
</tr>
<tr>
<td>Ahwai et al7</td>
<td>27</td>
<td>M</td>
<td>Yes</td>
<td>Normal</td>
<td>ND</td>
<td>ND</td>
<td>Negative</td>
<td>ONB</td>
<td>NS</td>
<td>Resolution</td>
</tr>
<tr>
<td>Ahwai et al7</td>
<td>27</td>
<td>M</td>
<td>Yes</td>
<td>190/120</td>
<td>Elevated</td>
<td>Positive</td>
<td>Negative</td>
<td>ONB</td>
<td>Resolution</td>
<td>Resolution</td>
</tr>
<tr>
<td>Osterman et al8</td>
<td>28</td>
<td>M</td>
<td>Yes</td>
<td>160/110</td>
<td>Elevated</td>
<td>Positive</td>
<td>Positive</td>
<td>ONB</td>
<td>Resolution</td>
<td>Resolution</td>
</tr>
<tr>
<td>Sigley et al10</td>
<td>33</td>
<td>F</td>
<td>No</td>
<td>Normal</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ONB</td>
<td>Resolution</td>
<td>Resolution</td>
</tr>
<tr>
<td>Singh et al11</td>
<td>17</td>
<td>F</td>
<td>No</td>
<td>140/95</td>
<td>ND</td>
<td>Positive</td>
<td>–</td>
<td>ONB</td>
<td>–</td>
<td>Death during treatment</td>
</tr>
<tr>
<td>Pope et al12</td>
<td>56</td>
<td>F</td>
<td>Yes</td>
<td>NS</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>ONB</td>
<td>Resolution</td>
<td>Resolution</td>
</tr>
</tbody>
</table>

M: Male, F: Female, ND: Not Done, NS: Not Stated
nasal NEC and SIADH has been established in previous reports.

REFERENCES