SIADH as a paraneoplastic syndrome of squamous cell carcinoma of the hypopharynx

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ABSTRACT

Introduction: Hypopharyngeal cancer is an uncommon malignancy, representing only 4.3% of head and neck cancers. It is usually found late in the course, accounting for its high five-year mortality. SIADH has been seen in other squamous cell cancers mainly of the lungs. Case Report: We report a case of profound hypotremia secondary to SIADH occurring in an elderly Vietnamese man in the setting of a large, well-differentiated squamous cell cancer of the hypopharynx. Conclusion: SIADH is a common occurrence in squamous cell cancer of the lung. It occurs in only 3% of head and neck tumors. The putative etiologies include direct carotid involvement by the tumor, carotid manipulation during operative dissection, and as a side effect of chemotherapy or radiation. In this case, SIADH preceded operative intervention and there was no carotid involvement of the tumor. SIADH is an uncommon occurrence in head and neck tumors despite majority of them being squamous cell cancers. Usual etiologies for SIADH in this setting include medication side effects and involvement or manipulation of the carotid artery. None of these factors were present in this case leading to the conclusion that SIADH was caused by the tumor itself.

Keywords: SIADH, Pharyngeal cancer, Paraneoplastic process

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INTRODUCTION

According to a National Cancer Database, hypopharyngeal cancer represents 4.3% of all head and neck cancers [1] and will affect 2500 patients annually [2]. Ninety-five percent of these are squamous cell cancers [3] with 5-year survival rates ranging from 20-50% depending on the site, the stage, and the interventions used in treatment [4]. It is more common among men, African Americans and individuals working with metal, cement, and stone and has an unclear relationship to asbestos [3]. It has been implicated in exposure to the defoliant Agent Orange (a 50:50 mixture of 2,4,5-T and 2,4-D) which was used extensively in the Vietnam War, but that link is far from established [5]. Additional risk factors include potential nutritional deficiencies [6] and chromosomal abnormalities including a loss of chromosome 18 [7] and an over-amplification of chromosome 11q13 [8].

Paraneoplastic syndromes have been previously described in association with multiple cancers. With squamous cell cancer, it is most often seen in malignancies of the lung, but has been described in squamous cell cancer of the pharynx. Paraneoplastic syndromes associated with pharyngeal cancer include hypercalcaemia [9], leukocytosis, vasculitis [10, 11], neuropathy [12], polymyositis [13] and the syndrome of
inappropriate antidiuretic hormone secretion (SIADH). In the latter, it is usually associated with direct carotid involvement or manipulation of the carotid [14, 15] or as a side-effect of chemotherapeutic agents or radiation [16]. The case below describes SIADH in the setting of a large hypopharyngeal cancer without the above causative features.

**CASE REPORT**

85-year-old Vietnamese male with history of COPD and previous tobacco abuse presented with a three month history of hemoptysis and cough recently treated with trimethoprim/sulfamethoxazole for bronchitis and three days of sore throat and shortness of breath. He denied fever, chills or chest pain. He admitted to decreased appetite and mild weight loss. Patient denied recent travel, history of tuberculosis, or sick contacts. There was no reported dysuria, polyuria or polydypsia.

Past medical history is significant for hypertension, hyperlipidemia, COPD and congestive heart failure. His medications at admission were: amlodipine 10 mg daily, metoprolol 100 mg twice daily, aspirin 81 mg daily, omeprazole 20 mg daily, albuterol/atrovent MDI 2 puffs, 3 times per day and simvastatin 40 mg at bedtime.

Admission laboratory test showed a Complete Metabolic Panel and a Thyroid Stimulating Hormone level as below (table 1). Chest X-ray demonstrated pulmonary hyperinflation. CT angiogram demonstrated COPD with bi-apical blebs but no lung mass nor hilar adenopathy.

Computed tomography (CT) of the neck showed a large mass in the hypopharynx nearly completely obliterating the airway. (figures 1, 2) Emergent

| Test                  | Result | Normal Range   |
|-----------------------|--------|----------------|
| Sodium                | 116    | 135 - 145 mmol/L |
| Potassium             | 4.5    | 3.6 - 5.2 mmol/L |
| Chloride              | 86     | 101 - 111 mmol/L |
| CO2                   | 23     | 23 mmol/L       |
| Blood Urea Nitrogen   | 21     | 9 - 21 mg/dL    |
| Glucose               | 163    | 70 - 110 mg/dL  |
| Calcium               | 8.3    | 8.4 - 10.2 mg/dL|
| Bilirubin- Total      | 0.4    | 0.2 - 1.2 g/dL  |
| Albumin               | 3.4    | 3.4 - 4.8 g/dL  |
| Alkaline Phosphatase  | 69     | 40 - 150 U/L    |
| Aspartate             | 18     | 5 - 40 IU/L     |
| Aminotransferase      |        |                 |
| Alanine Aminotransfer | 16     | 6 - 55 IU/L     |
| Thyroid Stimulating Hormone | 3.18 | 0.35 - 4.90 uIU/L |

| Test                      | Result | Normal Range   |
|---------------------------|--------|----------------|
| Serum Sodium              | 116 mmol/L | 135 - 145 mmol/L |
| Urine Sodium              | 68 mmol/L  |                 |
| Urine Osmolality          | 299 mOsm/kg | 220 - 1300 mOsm/kg |
| Serum Osmolality          | 257 mOsm/kg | 260 - 300 mOsm/kg |

Table 1. Admission laboratory findings.

Table 2. Preliminary evaluation for hyponatremia.

Figure 1 A, B): CT scan showing a large mass in the hypopharynx nearly completely obliterating the airways.
tracheostomy was performed and biopsy revealed a moderately-differentiated invasive squamous cell cancer. Given the extensive nature of his malignancy, patient was transferred to an area referral center for debulking procedure and definitive management.

DISCUSSION

Paraneoplastic syndrome was first described by a French physician in 1890 in relation to neurologic symptoms associated with cancer [17]. SIADH is well described in the literature in relation to small cell lung cancer and central nervous system tumors [18].

Talmi et al. in a retrospective review, found a 3% occurrence rate of SIADH in head and neck cancers [19]. There are many possible etiologies of SIADH in hypopharyngeal cancer. Carotid manipulation after resection of the malignancy or as a result of neck dissection for other malignancies is often seen and is presumed to be caused by stimulation of the baroreceptors associated with the carotid bulb [14, 15]. SIADH occurring with chemotherapy and radiation appear to be separate processes: the former as a medication effect [16, 20] and the latter theorized to be a radiation-induced compromise of cerebral blood flow leading to increased AVP production [21]. In this case, there was no clear carotid involvement on CT scan and no manipulation of the neck apart from the tracheostomy tube placement.

Diagnostic criteria for SIADH include: hyponatremia without evidence for volume overload, hypotonicity with plasma osmolality <270 mosmol/kg, inappropriately concentrated urine with urine osmolality >100 mosmol/kg, urine sodium level >40 meq/L, normal acid-base and potassium balance, normal adrenal and thyroid function, and correction of the hyponatremia with fluid restriction but not with 0.9% saline infusion [22].

The euvolemic hypo-osmolar hyponatremia was present on admission to the hospital and prior to his tracheostomy. This patient met all of the diagnostic criteria listed above. Serum and urine osmolality as well as urine sodium concentration were diagnostic and noted in table 2. Consistent with usual care, AVP levels were not measured. Rather, the patient was treated with the recommended intervention for SIADH which is fluid restriction and his sodium increased to the near-appropriate range of 132 mmol/L. As above, he was then transferred for staged de-bulking procedures at an area referral center.

CONCLUSION

Squamous cell cancer of the hypopharynx is an aggressive malignancy with a high five-year mortality rate. Like squamous cell cancers elsewhere it is associated with paraneoplastic syndromes, specifically SIADH. Unlike other published cases, however, this case of SIADH was not a result of carotid involvement, chemotherapy, nor dissection of the tumor. Rather, it appears to be a direct result of the tumor itself which is a rare occurrence for this uncommon malignancy.

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Author Contributions
Paul Hicks – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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