Esthesioneuroblastoma as a cause of syndrome of inappropriate antidiuretic hormone

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ABSTRACT
Esthesioneuroblastoma (ENB) is a rare neuroendocrine malignancy of the olfactory epithelium that infrequently presents with syndrome of inappropriate antidiuretic hormone (SIADH). We discuss the case of a 37-year-old woman with history of primary hypothyroidism and systemic lupus erythematosus (SLE) presenting with SIADH prior to the diagnosis of a left nasal cavity ENB (Kadish stage B, Hyams grade 1). Her SIADH diagnosis was obfuscated by concomitant discovery of a pituitary microadenoma, primary hypothyroidism, and adrenal insufficiency due to longstanding corticosteroid use for SLE. The ENB was discovered in the setting of recurrent epistaxis. The patient experienced resolution of her hyponatremia immediately following endonasal endoscopic tumor resection with negative margins. Workup for SIADH of unknown origin should include attention to sinus disease with MRI brain for the rare possibility of ENB. In patients with ENB with associated SIADH, repeat sodium levels may provide additional surveillance for recurrence.

Introduction
Esthesioneuroblastoma (ENB) or olfactory neuroblastoma is a rare malignant tumor of the neuroectoderm-derived olfactory epithelium that normally lines the superior nasal cavity and is responsible for reception of odorant stimuli. ENB frequently presents with non-specific symptoms of obstruction, facial pain/pressure, epistaxis, or hyposmia/anosmia, but less commonly has been associated with paraneoplastic syndromes, including syndrome of inappropriate antidiuretic hormone (SIADH) or ectopic adrenocorticotropic hormone (ACTH) production [1]. We describe a case of ENB diagnosis preceded by a complicated presentation of SIADH with resolution of hyponatremia following surgical removal.

Case
A 37-year-old woman with a history of systemic lupus erythematosus (SLE), hypothyroidism, and hyponatremia of unclear etiology presented due to recurrent large volume epistaxis requiring transfusion. The patient’s sodium was 123 mmol/L.

The patient’s hyponatremia had been incidentally discovered 2.5 years prior following routine labs during an unrelated hospitalization. She was diagnosed with SLE six months later. Shortly after, during hospitalization for a SLE exacerbation, magnetic resonance imaging (MRI) was performed for evaluation of her hyponatremia and revealed a 2.5 mm pituitary microadenoma and left paranasal sinus thickening thought to represent polypoid disease (Figure 1). The patient was determined to have hypothyroidism as well as secondary adrenal insufficiency (AI), likely due to long-standing treatment with corticosteroids for her SLE. However, after initiation of treatment for hypothyroidism and AI her hyponatremia did not resolve and, as such, it was thought that it could be secondary to her SLE [2]. Her sodium levels were maintained in the range of 126–130 mEq/L with fluid restriction and salt tablets.

Upon presentation with epistaxis, she endorsed congestion and facial pain/pressure with rhinorrhea, and decreased sense of smell for 1 month. On physical exam and nasal endoscopy, an obstructive, non-pulsatile mass was visualized in the left nasal cavity.
spanning from the nasal floor to the superior meatus. Biopsy of the lesion was performed due to suspicion for neoplasm. Histopathology of the lesion was consistent with ENB. Positron emission tomography (PET) scan showed no regional or distant disease, and the mass was staged as Kadish B. The patient was presented at a multidisciplinary tumor board, with surgical resection and adjuvant radiation recommended.

She underwent surgery two weeks later, and the tumor was removed using an endonasal endoscopic approach. Surgical pathology confirmed the lesion as a Hyam’s grade I ENB. Sodium trending showed resolution of the patient’s hyponatremia to normal values within the first 24 h post-operatively and her sodium remains in the normal range without any intervention.

**Informed consent**

The subject of this article has given consent for their medical information and images to be published in a scientific journal.

**Discussion**

The patient’s presentation was complicated by several factors including her hypothyroidism, adrenal insufficiency from chronic steroid use due to SLE, and an incidentally found pituitary microadenoma, obfuscating her SIADH and delaying ENB diagnosis for over 2 years. Her situation was unique in that she initially underwent an MRI to evaluate for an etiology for her hyponatremia. Although there was thickening along the left paranasal sinuses, otolaryngology consultation was not obtained due to her complicated presentation. Workup for SIADH of unknown etiology commonly includes MRI brain, imaging to rule out potential pulmonary causes and medication reconciliation, however, physicians may ask for the inclusion of the nasal cavity or sinuses in brain imaging to be able to evaluate for head and neck sources as well. Similarly, patients diagnosed with ENB should have their serum electrolytes checked prior to treatment.

The prevalence of SIADH in patients with ENB was conservatively estimated to be 2% by Gabbay.
et al. in 2013 based on 26 identified cases in the literature over an extrapolated 1300 total cases of ENB [3]. However, subclinical symptoms, failure to link hyponatremia with ENB, and a lack of reporting likely leads to an underestimation of prevalence. The exact mechanism of SIADH development is unclear but is related to ectopic production by the tumor, as multiple cases have shown the presence of arginine vasopressin in the excised tumor through immunohistochemical staining [4].

The majority of cases of SIADH due to ENB within the literature report resolution of SIADH after surgical resection [3]. As the half-life of ADH in serum is 10–35 min, resolution may occur in the immediate post-operative period. One case noted in the literature was treated through non-surgical methods due to concern for neurological deficits following radical resection with resolution of SIADH following 3 cycles of a chemotherapy regimen including etoposide, ifosfamide, and cisplatin [5]. While many cases of ENB presenting with SIADH are slow-growing, as evidenced by the delay in diagnosis in our case and others, there have been reports of high grade, late stage, more aggressive lesions presenting with SIADH [4,6].

For cases of ENB presenting with SIADH, sodium levels may be able to provide additional information on disease burden. In one previous case, a 10% remnant of ENB was noted on MRI following an initial surgical resection, and while the patient was able to decrease their supplementary sodium intake, their sodium levels remained low until a second intervention was performed [7]. This suggests that patients who do not see resolution of their SIADH following treatment should be screened for residual disease. Likewise, some groups have suggested the use of sodium screening to assess for recurrence in patients whose ENB showed concurrent SIADH. Plasencia et al. introduced the case of a patient who showed recurrence of their SIADH with ENB recurrence 16 years following the initial lesion [8]. Of note, hyponatremia was the first sign of recurrence, as the patient had no findings on routine follow-up examination or imaging. Gabbay et al. proposed the use of electrolytes and osmolality measured every 3 months during the first year of follow-up and every 6 months for the second to fifth years [3]. Although the evidence supporting this practice is limited due to the scarcity of the condition, it is a reasonable addition to the routine surveillance for this select group of patients.

In conclusion, patients with SIADH of unknown etiology should be evaluated for malignancy, especially if concurrent sinus or nasal cavity findings are noted on examination or imaging. In patients with ENB and associated SIADH, hyponatremia frequently resolves following ENB treatment with lack of hyponatremia correction likely signaling inadequate tumor resection. Serum sodium levels may be used as an additional mechanism for malignancy surveillance.

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**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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