INTRODUCTION

Originally described by Schwartz and Bartter in 1957 in 2 patients with bronchogenic carcinoma, the syndrome of inappropriate antidiuresis (SIAD) is caused by the persistent release of vasopressin (antidiuretic hormone) in the absence of the usual physiologic stimuli. The SIAD, also referred to as Schwartz—Bartter syndrome, is characterized by hypotonic hyponatremia in a euvoletic state, with ongoing water retention, natriuresis, and elevated urine osmolality despite decreased plasma tonicity and normal renal, adrenal, and thyroid functions. Less commonly, SIAD in the apparent absence of disease has been reported and is increasingly recognized in the elderly population as an important cause of chronic hyponatremia. However, to our knowledge, there have been no reports of idiopathic SIAD in young adults, and any such presumed cases have eventually been shown to be secondary to neoplastic process.

CASE PRESENTATION

A 23-year-old graduate student presented in September 2014 complaining of intermittent nausea and vomiting of 1 week’s duration. She was admitted for investigation and treatment, as her serum sodium was 111 mmol/l.

The patient’s past medical history was unremarkable, and her only regular medication consisted of the oral contraceptive pill (Alesse [levonorgestrel and ethinyl estradiol]), which she had taken for years. She had no smoking history and denied use of any illicit drugs. Her family history included a parent with chronic lymphocytic leukemia but was otherwise negative for any neurological, pulmonary, renal, or autoimmune disease.

The patient described having been in her usual state of health until 10 days earlier, when she developed symptoms of an upper respiratory tract infection, including pharyngitis, rhinorrhea, fatigue, and a mild headache after returning from a camping trip with her family. Three days later, she had developed nausea and vomiting that persisted intermittently for 1 week before her presentation. She continued to have mild headache and fatigue, for which she took ibuprofen (200 mg), and nausea, for which she took dimenhydrinate. Throughout the course of her illness, she denied ever having experienced photophobia, neck stiffness, vision changes, fever, chills, night sweats, weight loss, confusion, or seizures. She also denied polydipsia or any change in her thirst and drinking behavior.

On examination, she was alert and looked well. Her blood pressure was 118/84 mm Hg, heart rate was 83 beats/min, and temperature was 36.6 °C. She did not appear dehydrated, demonstrating moist mucous membranes, warm skin with good turgor, and a normal jugular venous pressure. She had no papilledema. Her cardiac, pulmonary, and abdominal examination results were within normal limits, and she exhibited no lymphadenopathy.

Laboratory data obtained at the time of admission showed a serum sodium of 111 mmol/l with a serum osmolality of 230 mmol/kg, urine sodium of 160 mmol/l, and urine osmolality of 764 mmol/kg (Table 1). Electrolytes measured 1 year earlier as part of a routine check-up had been normal. A diagnosis of SIAD was made.

Investigations

During her admission, serum creatinine, thyroid stimulating hormone, and cortisol levels were all...
within the normal ranges. CT scan of the patient’s chest was unremarkable, revealing no mass, lymphadenopathy, or other pathology. Magnetic resonance imaging of her head showed no structural abnormality, hemorrhage, or mass. The meninges were unremarkable, and the pituitary gland was normal in appearance, with a typical T1 hyperintense signal of the posterior lobe.

Management and Outcome
The patient’s fluid intake was restricted to 750 ml daily. After 36 hours, her serum sodium was 113 mmol/l and she remained symptomatic. She was then started on furosemide 20 mg twice a day and salt (NaCl) tablets 2 g twice a day in addition to fluid restriction. Over the next 4 days, serum sodium rose to 126 mmol/l, and the patient’s symptoms resolved completely. She was discharged and was placed on daily fluid restriction of 1 L and 1 g NaCl twice a day. Serum sodium was maintained at 135 to 138 mmol/l. A serum antidiuretic hormone level measured on an outpatient basis on November 5, 2014, after 1.5 hours of rest in supine position, was elevated at 4.2 pmol/l (reference range, 0.8–3.5).

Follow-up
Over the course of 2.5 years, our patient had 2 documented episodes of hyponatremia with one being severe enough to require hospitalization. Both episodes were associated with liberalization of fluid intake and withdrawal of salt supplements. A repeat serum antidiuretic hormone level was 3.9 pmol/l (reference range, 0.8–3.5). Imaging studies were performed at regular intervals to rule out an occult neoplastic process in her chest, abdomen, and brain, including the paranasal sinuses. High-resolution computed tomography of the chest and neck, magnetic resonance imaging of the brain and paranasal sinuses and abdomen, and a mammogram were all inconclusive. In January 2017, as a part of the continuing surveillance, she had a repeat magnetic resonance imaging of the brain, paranasal sinuses, and skull base that identified a lesion in the infundibulum of the left maxillary sinus. The lesion was of intermediate intensity on T2-weighted images and mildly enhancing; a component of this mass was seen protruding into the sinus, and a smaller component into the hiatus semilunaris (Figure 1).

The patient was referred to otolaryngology, and the decision was made to endoscopically resect the mass. She underwent surgery in September 2017. Intraoperatively, the mass was visualized in the lateral nasal osteomeatal complex. It should be noted that immediately postoperatively, the patient had to excuse herself to void.

Pathology
The biopsy samples showed an infiltrating tumor composed of small round cells within well-developed neuropils. Scattered tumor cells showed focal differentiation to larger neuronal cells. Immunohistochemistry revealed strong positivity for synaptophysin, chromogranin, neurofilaments, S-100, thyroid transcription factor-1, and vasopressin as well as scattered positivity for neuronal nuclei (Figure 2). The features of this tumor are those of a neuronal lesion classified as a neurocytoma; positivity for thyroid transcription factor-1 and vasopressin indicate hypothalamic differentiation. Consistent with the slow growth of this lesion, the Ki67 labeling index was 1.5%.

Postoperative Course
One month post-surgery, the patient’s serum sodium was in the normal range. She was not on any salt supplements or on any fluid restriction. A serum antidiuretic hormone level drawn after rest in the supine position for 1.5 h approximately 3 months post-surgery (December 2017) was 1.0 pmol/l (reference range, 0.8–3.5). One year post-

Table 1. Investigations during the first admission

| Test                  | Result     |
|-----------------------|------------|
| Hemoglobin            | 138 g/l    |
| WBCs                  | 6130 cells/µl |
| Platelet count        | 261 × 10^3/µl |
| Serum Na⁺              | 111 mmol/l |
| Serum Cl⁻              | 95 mmol/l  |
| Serum K⁺               | 4.3 mmol/l |
| Serum HCO₃⁻             | 22 mmol/l  |
| Anion gap              | 12         |
| Serum glucose          | 5.3 mmol/l |
| Serum urea             | 2.5 mmol/l |
| Serum creatinine       | 59 µmol/l  |
| Serum Ca²⁺ (total)     | 2.14 mmol/l|
| Serum PO₄³⁻             | 1.1 mmol/l |
| Serum Mg²⁺             | 0.68 mmol/l|
| Urine Na⁺              | 160 mmol/l |
| Urine K⁺               | 110 mmol/l |
| Urine osmolality       | 764 mmol/kg |
| Plasma osmolality      | 230 mmol/kg|
| Osmolality gap         | 4.0        |
| Serum albumin          | 43 g/l     |
| Serum total protein    | 68 g/l     |
| β-Hydroxybutyrate      | 0.4        |
| β-HCG                  | <1.0       |
| TSH                    | 1.7 µU/l   |
| Serum cortisol (AM)    | 550 nmol/l |
| Serum renin            | 2.9 pmol/l |
| ALT                    | 49 IU/l    |
| AST                    | 32 IU/l    |
| Alkaline phosphatase   | 49 IU/l    |
| GGT                    | 13 IU/l    |
| Amylase                | 114 IU/l   |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AM, ante meridiem; GGT, γ-glutamyl transpeptidase; HCG, human chorionic gonadotropin; TSH, thyroid-stimulating hormone; WBC, white blood cells.
surgery, serum sodium is normal, and diet and fluid intake are normal. Follow-up by otolaryngology shows no evidence of tumor recurrence.

**Final Diagnosis**

The final diagnosis was SIAD secondary to an ectopic hypothalamic neurocytoma in the left maxilla.

**Figure 1.** Magnetic resonance image of paranasal air sinus demonstrating tumor arising from the left maxillary sinus. A T2 intermediate mass is seen in the left maxillary sinus (yellow arrows).

**Figure 2.** Histopathology of excised maxillary tumor. (a) The tumor from the maxillary sinus was composed of solid nests and sheets of small cells underlying the respiratory mucosa (right). (b) Higher magnification shows the small tumor cells with scattered larger cells within a fibrillary stroma. (c) The tumor cell nuclei stain for neuronal nuclei, and (d) there is strong reactivity for neurofilaments, confirming the neuronal nature of this tumor. (e) The nuclei of this tumor show extensive reactivity for thyroid transcription factor-1, a biomarker of the basal hypothalamus, and (f) the tumor cells express vasopressin. These are features of hypothalamic neurons. The various marker reagents are listed in Maguire et al. Brown color indicates positive antibody reactivity.
Since its identification in 1957, SIAD has been associated with several conditions including malignancy, cerebral insult, cerebrovascular disease, infection, pulmonary disease, and various drugs. The existence of an idiopathic form of this syndrome has been suggested in the past, and cases without an identifiable etiology have been poorly documented in the literature. Over the past 20 years, idiopathic SIAD as a specific disease entity has garnered more acceptance as a diagnosis of exclusion, particularly in the elderly population, where it has been most commonly observed. For instance, Miller et al. reported that, of 27 patients in an outpatient geriatric clinic diagnosed with SIAD, 7 (26%) were considered to have an idiopathic form of the syndrome.

Our patient was diagnosed with “idiopathic” SIAD, but after extensive workup for 2.5 years, the cause of her SIAD eventually surfaced in the form of a neurocytoma in the maxillary sinus. Hypothalamic neurocytoma producing vasopressin, presenting as SIAD, has been reported in the region of the sella turcica. Our case is particularly interesting because of the unusual location of this tumor. The paranasal sinuses are more commonly the site of a related tumor, olfactory neuroblastoma, which resembles neurocytoma morphologically. Because of the similar histopathological characteristics and paranasal sinus location, we considered the diagnosis of olfactory neuroblastoma. However, the production of vasopressin as well as expression of thyroid transcription factor-1, a biomarker of tissues derived from the basal hypothalamus, make this more likely to be an ectopic hypothalamic neurocytoma (Table 2). To date, however, there is insufficient information as to whether olfactory neuroblastomas express thyroid transcription factor-1.

### DISCUSSION

Table 2. Teaching points

|   |   |
|---|---|
| 1. | Idiopathic SIAD is a diagnosis of exclusion. |
| 2. | A thorough investigation must be done before labeling a patient as having idiopathic SIAD. |
| 3. | Serum ADH levels should not be used routinely for diagnosis of SIAD. |
| 4. | Repeated high levels of ADH ruled out gain-of-function mutation in gene encoding the V2 receptor (AVPR2; 300538) on chromosome Xq28 (typically a disease of neonatal age group). |
| 5. | Ectopic hypothalamic neurocytoma is an exceedingly rare cause of SIAD. |
| 6. | In our case, the tumor was found to be the culprit, as it showed strong immune reactivity to TTF-1 and vasopressin. |
| 7. | After removal of the tumor, there was spontaneous improvement in the serum sodium levels. |
| 8. | Recurrence of hyponatremia and resurgence of high ADH levels (in the absence of other trigger factors) could be potentially used as a marker of recurrence of the tumor. |
| 9. | Finally, the attention to persistent surveillance imaging, searching for the proverbial “needle in the haystack,” led to the successful diagnosis. |

ADH, antidiuretic hormone; SIAD, syndrome of inappropriate antidiuresis; TTF-1, thyroid transcription factor-1.

*Based on Feldman et al.*

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