Introduction

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or Schwartz-Bartter syndrome is characterised by excessive levels or activity of arginine vasopressin (AVP) with hyponatraemia and hypomosmolality. High urinary sodium concentration without salt and water intake alterations is present. Usual causes of SIADH are drugs, intracranial pathology, trauma and predominantly paraneoplastic syndromes. Most commonly paraneoplastic syndrome is related to small-cell carcinoma of the lung. Many studies have also been conducted about incidence of SIADH in head and neck cancer reporting 3% of patients affected by apparently idiopathic hyponatraemia. Most tumours are squamous cell carcinomas, but a small number of neuroendocrine sinonasal carcinomas have been reported. The prevailing phenotype is esthesioneuroblastoma (ENB) or olfactory neuroblastoma, first described by Berger in 1924, which is known to be capable of producing biologically active substances such as somatostatin, calcitonin and vasoactive polypeptides. Olfactory neuroblastoma has been reported to be responsible for development of SIADH, especially in young patients.

Case report

A 31-year-old man was admitted to a North American hospital with complaints of nausea, dizziness and weak-
ness for about a week. The patient was seen in an Urgent Care Centre and at physical examination temperature, heart rate, blood pressure and other vital criteria were normal: no cervical lymphadenopathy, no oedema was noted. The laboratory data reported a hypotonic hyponatraemia (serum sodium 111 mmol/L, serum osmolality 237 mmol/kg) in a euvolemic, non-oedematous patient with normal levels of potassium, chloride, bicarbonate and creatinine. Urinary sodium was 58 mmol/L, urinary osmolality was 266 mmol/kg. The patient’s hyponatraemia was interpreted as a chronic disease given the fact that even with a sodium of 111 mmol/L on admission he had no change in mental status. He was treated with fluid restriction and furosemide for 2 days but his sodium increased to only 116. As patient continued to remain hyponatraemic despite resolution of nausea and pain, a CT scan of head, neck, chest and abdomen was performed, demonstrating a homogeneous mass lesion that expanded the right ethmoid. No evidence of lung masses or adenopathy were found. ENT consult was obtained and differential diagnosis was reported as a malignant lesion versus aggressive fungal infection. The patient was started on demeclocycline to inhibit ADH action with an increase in sodium to 129 on the day of discharge. A few days later an endoscopic biopsy of the right sinonasal mass under local anaesthesia was performed. At microscopic examination, the tumour was highly cellular and composed of round to oval neoplastic cells with slight nuclear pleomorphism and scant cytoplasm, organised in solid nests with sparse Homer-Wright rosettes. Scattered mitotic figures (up to 8 x 10 high power fields (HPF)) but no necrosis were found (Fig. 1). The proliferative index was 20% (MIB1/Ki-67). The neoplastic cells were stained positively with synaptophysin, chromogranin, NSE and CD56-NCAM. No immunostaining was observed for AE1/AE3, Cam 5.2 and Bcl-2. These findings, together with the morphology, were consistent with the diagnosis of olfactory neuroblastoma.

The patient at this point made return to his home country and was admitted to our hospital for therapeutic planning. MR scan of the head and neck was performed (Fig. 2 A-B), results were consistent with the CT data, additional information were precise dimensions (38x16 mm), slight nasal septum and nasolacrimal duct deformation. Endoscopic nasal evaluation was performed (Fig. 2C). According to Kadish grading\(^9\), the lesion was classified as stage B. After tumour board discussion, an endoscopic resection of the lesion without lamina cribra resection and duroplasty was performed (Fig. 2D). Serum natraemia levels normalised the day after surgery. Postoperative radiation therapy was administered. The patient underwent regular endoscopic and radiological follow-up and 5 years later is disease-free.
Discussion

Over the past 45 years 17 cases of SIADH associated with olfactory neuroblastoma were reported. In all cases, the secretion of the neurohypophysial hormone manifested itself prior to the diagnosis of ONB. In most cases, the time between first determination of hyponatraemia and detection of the sinonasal mass was short, thus allowing to consider the two aspects concomitants. Limited reports demonstrate preexisting SIADH, in a patient otherwise asymptomatic, which was accordingly considered idiopathic for months to years.

Only in a few of the above-mentioned studies was AVP secretion directly demonstrated on frozen section sections, most commonly the relationship between high blood levels of AVP and aberrant neuroendocrine tumour secretion was considered consequential as natraemia rapidly increased to standard levels after successful treatment of ONB. In the totality of the reports, in fact, natraemia levels normalised immediately after ONB treatment was accomplished, independently from the oncologic outcome of the patient.

An interesting aspect, already mentioned by Gray and colleagues is the relatively young age of the small group of patients affected by this peculiar clinical lesion: average age at diagnosis was 37 years. Olfactory neuroblastoma mainly arises in two decades, the second and the fifth, although it is most commonly reported around the fiftieth year.

SIADH as a paraneoplastic syndrome most commonly is related to small cell carcinoma of the lung and it reveals itself usually as a mild clinical picture. The accidental detection of a slight natraemia alteration, in fact, often leads to pulmonary investigation and allows to connect the two clinical aspects. On the contrary, as previously noticed, most of the diagnoses of idiopathic hyponaetraemia which revealed the neuroendocrine nasal disease were accomplished for severe nervous or systemic diseases. Nonetheless, in our opinion, even in the presence of mild clinical case it is advisable to suspect early a sinonasal involvement after pulmonary lesions are excluded, especially in young patients.

In a previous report, alterations in serum sodium metabolism preannounced an olfactory neuroblastoma relapse, 16 years after first diagnosis, with no history of SIADH at the time of the first diagnosis. Pathological hyponaetraemia and late lymph nodal relapse were reported as well. This aspect leads to consider that natraemia is a valuable follow-up tool in patients affected by olfactory neuroblastoma, with or without history of SIADH. Serum sodium evaluation is also an inexpensive, practical exam that can be easily performed during follow-up.

Conclusions

In patients affected by idiopathic SIADH, after a pulmonary primitive lesion has been excluded, the study of the sinonasal area must be included in diagnostic work-up. In patients with history of ONB, it is advisable to continue follow-up lifelong to detect late recurrences as early as possible, which unfortunately are very common in neuroendocrine tumours. Along with clinical and radiological inspection, we found that periodic natraemia evaluation is useful as an inexpensive, smart and safe means to detect ectopic production of AVP. SIADH, in fact, can arise as an indirect sign for ONB recurrence even if not assessed at first diagnosis.

Table I. Reported cases of SIADH secondary to olfactory neuroblastoma.

| Author | Age/Sex | Presentation | Tissue demonstration of AVP secretion |
|--------|---------|--------------|--------------------------------------|
| Bouche 1967 | 34/M | Concomitant | No |
| Singh 1980 | 17/F | Concomitant | Yes |
| Pope 1980 | 56/F | Concomitant | No |
| Singley 1983 | 33/F | SIADH (4 years earlier) | No |
| Wade 1984 | 59/F | Concomitant | No |
| Osterman 1986 | 28/M | SIADH (6 years earlier) | Yes |
| Cullen 1986 | 26/F | SIADH (10 years earlier) | Yes |
| Myers 1994 | 79/F | Concomitant | No |
| Al Atwal 1994 | 27/M | Concomitant | No |
| Bernard 2000 | 22/M | Concomitant | Yes |
| Muller 2000 | 47/M | SIADH (15 months earlier) | No |
| Miura 2001 | 56/M | Concomitant | Yes |
| Plasencia 2006 | 34/F | SIADH unmasked ONB relapse after 16 years | No |
| Renneboog 2008 | 28/F | SIADH (6 months earlier) | No |
| Gray patient 1 2012 | 29/M | SIADH (5 months earlier) | Yes |
| Gray patient 2 2012 | 25/F | SIADH (3 months earlier) | Yes |
| Gray patient 3 2012 | 32/F | SIADH (8 months earlier) | Yes |
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Address for correspondence: Lucidi Daniela, Catholic University of Sacred Heart, Institute of Otolaryngology, largo Francesco Vito 1, 00168 Rome, Italy. Tel. +39 06 30154439. Fax +39 06 3051194. E-mail: dani.lucidi@gmail.com

Received: March 12, 2016 - Accepted: December 13, 2016