

Olfactory neuroblastoma (ONB) is a rare malignant neoplasm of sinonasal tract, derived from olfactory epithelium. Unilateral nasal obstruction, epistaxis, sinusitis, and headaches are common symptoms. Olfactory neuroblastoma shows neuroendocrine differentiation and similarly to other neuroendocrine tumors can produce several types of peptic substances and hormones. Excess production of these substances can be responsible for different types of endocrinological paraneoplastic syndromes (PNS). Moreover, besides endocrinological, in ONB may also occur neurological PNS, caused by immune cross-reactivity between tumor and normal host tissues in the nervous system. Paraneoplastic syndromes in ONB include: syndrome of inappropriate ADH secretion (SIADH), ectopic ACTH syndrome (EAS), humoral hypercalcemia of malignancy (HHM), hypertension due to catecholamine secretion by tumor, opsoclonus-myoclonus-ataxia (OMA) and paraneoplastic cerebellar degeneration. Paraneoplastic syndromes in ONB tend to have atypical features, therefore diagnosis may be difficult. In this review, we described initial symptoms, patterns of presentation, treatment and outcome of paraneoplastic syndromes in ONB, reported in the literature.

Key words: olfactory neuroblastoma, paraneoplastic syndromes, vasopressin, catecholamines, ACTH.

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Paraneoplastic syndromes in olfactory neuroblastoma

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Introduction

Olfactory neuroblastoma (ONB) is a rare malignant neuroectodermal tumor, comprising about 2% of all sinonasal tract tumors. Olfactory neuroblastoma is thought to arise from the specialized sensory neuroectodermal olfactory cells that are normally found in the upper part of the nasal cavity, including the superior nasal concha, the upper part of the septum, the roof of the nose, and the cribriform plate of ethmoid. Olfactory neuroblastoma may occur at any age, but demonstrates a bimodal peak of occurrence in the second and sixth decades of life without specific gender predilection. Unilateral nasal obstruction, epistaxis, sinusitis, and headaches are common symptoms. Delay in diagnosis is very frequent due to benign and nonspecific symptoms [1]. Olfactory neuroblastoma may mimic almost all tumors in the head and neck region, being described by Ogura *et al.* as a “great impostor” [2]. In one retrospective study, a review of 12 patients who were admitted to a single institute within two years and diagnosed with ONB was performed. After stringent neuropathology review, it turned out that the diagnosis was correct in only one in two patients [3].

Histologically, ONB is composed of small, round, blue cells, with a very high nuclear to cytoplasmic ratio, which are organized in lobules surrounded by sustentacular cells. Hyams’ grading system separates tumors into 4 grades. This scale is based on architecture, Flexner-Wintersteiner rosettes, Homer-Wright pseudo-rosettes, calcifications, fibrillar matrix, pleomorphism, necrosis and mitotic activity. However, ONB is often separated into low-grade (Hyams’ grade I and II) and high-grade (Hyams’ grade III and IV) in order to correlate grade with outcome. Low grade tumors have an 80% 5-year survival, while high grade tumors have a 40% survival [4].

The first and most common staging system was developed by Kadish [5]. It divides tumors into 3 groups. In group A, the tumor is limited to the nasal cavity; in group B, the tumor is localized to the nasal cavity and paranasal sinuses; and in group C, the tumor extends beyond the nasal cavity and paranasal sinuses. Morita modified this system, adding a fourth tier (D), which consists of local and distant metastases [6]. Another known classification is the Dulguerov *et al.* staging system, which is based on the TNM scale [7]. Nevertheless, no single staging classification has been universally adopted for this tumor to date, as the prognostic utility of each system has not been proven [5, 8].

Due to rarity of ONB, there are no specific treatment guidelines. However, usually craniofacial resection followed by radiotherapy is used in treatment of primary low- to moderate-grade lesions, with the addition of chemotherapy in patients with advanced, recurrent, or metastatic disease [4].

The main immunohistochemical findings include synaptophysin, chromogranin A, CD56, neuron-specific enolase (NSE), neurofilament proteins (NFP) and S-100 protein, which confirmed neuroendocrine differentiation in ONB [9]. Although most of the neuroendocrine tumors produce and secrete a large number of peptide hormones and amines, which can cause a spe-

cific clinical syndrome, most ONBs belong to so-called “non-functioning” tumors [10].

Although rare, ONB may be associated with paraneoplastic syndromes (PNS). Signs and symptoms in PNS do not result from direct tumor invasion or compression, but are related to tumor secretion of some peptides and hormones or immune cross-reactivity between tumor and normal host tissues [11]. To our knowledge, in ONB, endocrinological (syndrome of inappropriate ADH secretion – SIADH, ectopic ACTH syndrome – EAS, humoral hypercalcemia of malignancy – HHM, hypertension due to catecholamine secretion by tumor) and neurological PNS (opsoclonus-myoclonus-ataxia – OMA; cerebellar degeneration) may occur. In this review we describe the clinical characteristics of paraneoplastic syndromes reported in the literature, focusing on the diagnostic process and treatment options.

Endocrinological paraneoplastic syndromes

Ectopic ACTH syndrome

Ectopic ACTH syndrome is a PNS which can be associated with variety of solid tumors, mostly of neuroendocrine origin. The usual location is the chest, and the most frequent pathologies are small cell lung carcinoma (SCLC) and bronchial carcinoid. Less frequent causal tumors are thymic carcinoids, pancreatic islet cell tumors, pheochromocytomas, paragangliomas and medullary thyroid carcinomas [12].

Paranasal sinuses are not a common location for EAS, although there are a few cases of ACTH-producing tumors that originate from this area [13]. To our knowledge, 18 cases of ACTH-secreting ONBs have been described in the world literature (Table 1).

Ectopic pituitary adenomas are other reported cephalic pathologies associated with Cushing’s syndrome (CS). Because of the proximity to the sella, ONBs must be distinguished from pituitary adenomas that have extended downward into the nasal cavity or mentioned intracranial “ectopic” pituitary adenomas which originate from remnant cells deposited along the Rathke’s pouch developmental route and may develop into hormonally active adenomas in the ectopic regions, such as the sphenoid or cavernous sinus [14]. ACTH-secreting neuroendocrine tumors such as nasal paragangliomas [15, 16], ACTH-secreting nasopharyngeal carcinoma and meningioma [13] are other described paranasal and cranial ectopic sources of ACTH.

Usually rapid development of symptoms is characteristic of EAS, but not for pituitary adenomas. Weight loss rather than gain, fewer manifestations of cortisol excess, frequent manifestations of mineralocorticoids excess, hyperpigmentation, myopathy and hypokalemic alkalosis tend to be typical features of EAS [1].

There are two main types of EAS. The first is associated with clinically evident malignancies; a classic example of this entity is SCLC. The second type is secondary to a clinically occult neoplasm, with bronchial carcinoid being the classical example. Occult ACTH-secreting tumors frequently present a clinical picture similar to that seen with pi-

tuitary-dependent Cushing’s disease (CD), whereas overt tumors present atypically, with muscle wasting and weight loss being more frequently observed than the classic signs of hypercortisolism, such as moon face, truncal obesity, purple striae, etc.

The differences between types of EAS may result from molecular features. Carcinoid cells express the POMC gene like pituitary corticotroph cell, transcript pituitary like, 1200-nt, POMC mRNA and process the precursors to release large amounts of bioactive ACTH. In comparison, SCLC processes POMC in an aberrant way, producing low levels and altered molecular forms of POMC RNA, releasing high concentrations of “big ACTH” and less intact ACTH in the circulation [17]. Unfortunately, there are no studies about POMC processing in ACTH-secreting ONBs.

Ectopic ACTH syndrome associated with ONB could not be matched with either the first or the second type. In 9 cases, CS developed simultaneously with ONB diagnosis or its recurrence, in 5 in previously diagnosed evident ONB. However, in 4 cases, the location of the ACTH-secreting tumor was occult (median for interval between first CS symptoms and ONB diagnosis = 18 months). In ONB weight loss was reported in only 1 patient, myopathy in 5 out of 18, whereas weight gain was noted in 10 out of 18 patients, moon face in 9 out of 18, and red striae and purpura in 7 out of 18. Hypokalemia and metabolic alkalosis, which are more frequently found in both types of EAS than in CD, occurred in 11 out of 18 patients. Olfactory neuroblastoma may present a unique profile of CS manifestation, in which symptoms are rather similar to pituitary-dependent disease, while tumor is often overt [18].

ACTH-secreting ONB is an extremely rare cause of EAS, so one cannot be aware of the existence of this association from the very beginning of the diagnostic process. This diagnosis is very difficult for several reasons. First, despite the fact that the most accurate method of distinguishing between pituitary ACTH secretion and EAS is known to be IPSS, ONB might cause a false positive result more frequently when this method is used. This is a consequence of tumor location in the ethmoid sinus, which adjoins the upstream of the pituitary venous drainage system [19]. Generally, false positive results of IPSS may result from ectopic corticotropin-releasing hormone (CRH) secretion by the tumor, which stimulates ACTH production by the pituitary cells, or when there is a tumor with intermittent ACTH secretion or adrenal tumors with intermittent cortisol production, which could incompletely suppress endogenous ACTH production [20].

The CRH stimulation test and HDDST also help to distinguish EAS from a pituitary adenoma. Corticotropin-releasing hormone stimulation tests give a more accurate result than HDDST; however, among the reported cases of EAS associated with ONB, only a few reported the results of the CRH stimulation test [21]. One of them, diagnosed as ACTH-secreting ONB, showed increased ACTH levels after CRH stimulation, which might have led to a misdiagnosis of Cushing’s disease. Only 4% of patients with EAS respond to CRH. However, plasma ACTH and cortisol were non-suppressible to high-dose dexamethasone, but IPSS showed a high central-to-peripheral ratio of ACTH level [19,

Table 1. Case reports of olfactory neuroblastoma with ectopic ACTH syndrome

Study	Age	Sex	Symptoms	Treatment	Treatment at relapse	Outcome
Reznik <i>et al.</i> [28]	48	female	CS 28 months after initial treatment	surgery, chemotherapy	–	DDD
Fish <i>et al.</i> [36]	45	male	epistaxis, pneumonia, weight loss, lower-extremity swelling, polyuria, blurred vision, generalized weakness, hypokalemia, hyperglycemia	ketoconazole	–	lost to follow-up;
Yu <i>et al.</i> [26]	36	male	hypertension, hyperglycemia, pedal edema, proximal muscle weakness, mental confusion, hypokalemic alkalosis, facial plethora, buffalo hump, supraclavicular fat deposition, central obesity	metyrapone, radiotherapy	–	CS symptoms resolved
Arnesen <i>et al.</i> [37]	36	female	moon face, hyperglycemia, hypertension, hypokalemia, central obesity, proximal muscle weakness, hyperpigmentation	polypectomy	recurrence of tumor and CS surgery	CS symptoms resolved
Kanno <i>et al.</i> [22]	39	female	systemic edema, general fatigue, moon face, central obesity, pulmonary infection, hypertension, severe hypokalemia, and metabolic alkalosis	metyrapone, dexamethasone, tumor resection, local irradiation	maxillary sinus resected	CS symptoms resolved
Josephs <i>et al.</i> [25]	48	male	leg edema, blurred vision, general weakness, hypertension, hyperpigmentation, moon face, hypokalemic metabolic alkalosis	ketoconazole, surgery, radiation	–	CS symptoms resolved
Koo <i>et al.</i> [19]	66	female	systemic edema, general fatigue, moon face, central obesity, thin skin with purpura and hirsutism, hypokalemia, metabolic alkalosis	patient refused surgery	ketoconazole, craniotomy, adjuvant radiotherapy	CS symptoms resolved
	37	female	moon face, central obesity, proximal muscle weakness, hirsutism, hypertension,	etoposide, ifosfamide, cisplatin, radiotherapy	–	CS symptoms resolved
Mintzer <i>et al.</i> [1]	70	male	fatigue, confusion, severe hypertension, proximal muscle weakness, hyperglycemia, hypokalemia, metabolic alkalosis	ketoconazole, surgery, chemoradiotherapy	ketoconazole and octreotide	CS symptoms resolved
Han <i>et al.</i> [27]	59	male	nasal congestion, tearing, periorbital edema, neck swelling, hypokalemia, hypertension, hyperglycemia.	ketoconazole, chemotherapy, bilateral adrenalectomy, surgery	–	CS symptoms resolved
Hodish <i>et al.</i> [13]	48	male	leg edema, blurred vision, muscle weakness, hypokalemia, metabolic alkalosis, facial swelling, hyperpigmentation	ketoconazole, surgery, radiotherapy	–	CS symptoms resolved
	30	female	weight gain, moon face, skin changes, hypertension, amenorrhea, hirsutism, psychological changes, insomnia, buffalo hump, hyperpigmentation, acanthosis nigricans, tinea versicolor	surgery	–	CS symptoms resolved
Lin <i>et al.</i> [34]	64	female	general weakness, ulcerative herpes zoster patches, intractable herpetic neuralgia pain, altered mental testing, moon face, prominent supraclavicular fat pads, truncal obesity, hypertension, pneumonia, hypokalemia	antibiotics, meropenem	–	DDD
Butt and Olczak [31]	52	male	rhinorrhea, nasal obstruction, epistaxis, generalized weakness, bilateral ankle edema, hypokalemic metabolic alkalosis	surgery	metyrapone	CS symptoms resolved
Galioto <i>et al.</i> [29]	3	male	moon face, central obesity, asthenia, hirsutism	surgery	surgery	CS symptoms resolved
Rodgers <i>et al.</i> [30]	51	male	hypertension, arm pain, anosmia, nasal congestion, hypokalemia	surgery, radiotherapy	tumor resection, spironolactone	CS symptoms resolved
Inagaki [23]	33	male	dysgeusia, adynamia, stomatitis, facial and extremity edema, diarrhea, anxiety, irritability, insomnia, psychomotor excitement	surgery	chemotherapy, metyrapone	CS symptoms reappeared
Mayur [35]	19	male	weight gain, pruritic skin rash, purple striae on both arms and the abdomen	chemotherapy, surgery, radiotherapy	–	CS symptoms resolved

CS – Cushing's syndrome; DDD – death due to disease; NI – no information

22]. Anatomical location of the ACTH-secreting neuroblastoma may cause misleading IPSS results. Therefore, Kanno *et al.* recommend selective sampling from the cavernous sinus rather than the inferior petrosal sinus to avoid confusion [22]. Moreover, in the other case, both HDDST and CRH stimulation tests had suggested pituitary ACTH-dependent CS, until IPSS revealed EAS [13]. Suppression of POMC gene transcription in the tumor cells requires higher doses of glucocorticoids than in the pituitary, but in some cases the mechanism may work normally. That is why, in some patients with the EAS, cortisol levels are suppressed after 8 mg dexamethasone, as it occurs in pituitary CD [17]. On the other hand, Inagaki suggested that in one case of EAS secondary to ONB there was positive feedback regulation between cortisol and ACTH in the tumor. In this case, Decadron (dexamethasone), used with chemotherapy, may have triggered ACTH secretion by means of positive feedback regulation [23]. Immediate normalization in cortisol and ACTH levels as a response to metyrapone, which can inhibit production of cortisol but not ACTH directly, supports this hypothesis. It follows that the results of diagnostic procedures performed during EAS secondary to ONB could be very confusing and unclear.

Somatostatin receptor scintigraphy could be useful in diagnosing ACTH-secreting tumors. Octreotide is a somatostatin analogue that binds to the somatostatin receptors. The octreotide radionuclide scans are sensitive in identification of somatostatin receptor-expressing tumors, which constitute up to 80% of ectopic ACTH-secreting tumors, but they are not helpful when these receptors are absent. The therapeutic response to octreotide cannot be predicted by the results of an octreotide scan [24]. Diagnostic use of octreotide was reported in five cases of ACTH-secreting ONB which revealed tracer uptake corresponding to the ONB in all of them [1, 13, 23–26]. Octreotide with ketoconazole was also used therapeutically to suppress hypercortisolemia in three ONBs associated with EAS with different results: in all cases serum ACTH concentration was reduced, but it remained elevated [1, 19, 27].

In 16 of the reported ACTH-secreting ONBs, performed tests on the biopsy samples or excised tumors included ACTH immunohistochemical staining. Histologically there was no reported difference between ACTH-secreting and ACTH-nonsecreting ONB. In 14 cases the results of ACTH immunohistochemical staining were positive. Only in two cases did the clinical features of EAS occur despite negative staining for ACTH [19, 28]. In the first case, the symptoms disappeared when the tumor was resected, but in the second the patient died.

One pediatric case of CS secondary to ONB was reported by Galioto in a 3-year-old boy. He underwent endoscopic surgery of ONB at the age of 10 months and had already had elevated cortisolemia and moon face; however, there was no diagnosis of CS. At the age of 28 months, CS symptoms appeared with high levels of serum ACTH and cortisol in the laboratory findings. MRI revealed a right lymph nodal mass. After a right parapharyngeal lymphadenectomy the symptoms of CS disappeared [29]. Cushing's syndrome associated with ONB relapse has been described several times in adults. Arnesen reported recurrence of

both ONB and CS, which occurred 5 years after initial treatment, whereas first signs of EAS connected with ONB relapse have been reported four times [1, 23, 30, 31].

The majority of reported ACTH-secreting ONB had a favorable outcome, probably because the clinical manifestations of CS led to an earlier diagnosis and treatment. Only two patients died. It is possible that the ability to synthesize and secrete ACTH required a more differentiated and less aggressive tumor [13]. However, in other tumors development of CS may be an adverse prognostic factor, as in SCLC [32]. An unfavorable outcome in patients with SCLC and ectopic ACTH secretion results mainly from associated bacterial or opportunistic infections [33]. Severe infections during the course of EAS in ONBs occurred in 5 patients. Interestingly, Han *et al.* carried out bilateral adrenalectomy in a patient with recurrent infections of the colostomy site and other life-threatening complications due to EAS secondary to ONB, and his condition significantly improved [27].

Syndrome of inappropriate ADH secretion

Syndrome of inappropriate ADH secretion is a condition in which excessive release or action of ADH results in persistent hyponatremia and inappropriately elevated urine osmolality. Syndrome of inappropriate ADH secretion is the most common cause of hyponatremia and is responsible for one third of all cases [38]. There are various mechanisms leading to SIADH. It usually results from increased secretion of ADH by the pituitary gland or ectopic secretion from another source. Other mechanisms include increased sensitivity to ADH in the kidney, exogenous administration of ADH or desmopressin, cachexia, AIDS, and many more [39]. Differential diagnosis includes conditions in which euvoletic hyponatremia occurs such as hypothyroidism and glucocorticoid deficiency [40]. Hyponatremia may also result from cerebral salt wasting (CSW). In CSW the patient is truly volume contracted and has inappropriate natriuresis. It is important to distinguish between CSW and SIADH, because of different treatment algorithms. There is one case of CSW in a patient with a history of ONB. An MRI of the patient's brain revealed two basal frontal lobe lesions; nevertheless, biopsy revealed only necrotic tissue without any evidence of malignancy [41].

The symptoms of SIADH are mostly neurological and depend on both the degree of hyponatremia and the rate at which hyponatremia develops. When hyponatremia develops slowly, patients may be asymptomatic or have nonspecific symptoms such as anorexia, nausea, vomiting, irritability, headaches, and abdominal cramps. On the other hand, when hyponatremia occurs rapidly, patients tend to have more severe symptoms. When the serum sodium level is below 120 mEq or serum osmolality is less than 240 mOsm/kg, patients can experience cerebral edema, regardless of the rate of decrease. It may manifest as headache, nausea, restlessness, irritability, muscle cramps, generalized weakness, depressed reflexes, confusion, coma, or seizures. Serious neurological complications such as permanent brain damage, brainstem herniation, or respiratory arrest may occur [39].

In cancer patients, ectopic secretion of ADH by tumor cells causes paraneoplastic SIADH. This condition has been associated with SCLC, bronchogenic carcinoma, duodenal tumors, pancreatic tumors, thymus tumors, sarcoma, malignant histiocytosis, mesothelioma, and other occult tumors [39]. Syndrome of inappropriate ADH secretion has been reported in 1.5 to 3% of patients with head and neck cancer [42]. It may accompany squamous carcinomas, ONBs, small cell neuroendocrine carcinomas, adenoid cystic carcinomas, and undifferentiated carcinomas and sarcoma. Malignancies of the head and neck related to SIADH have most often been located in the oral cavity, and less often in the larynx, nasopharynx, hypopharynx, nasal cavity, maxillary sinus, parapharyngeal space, salivary glands, and oropharynx [43].

Since the first description in 1967 [44], there have been 35 cases of SIADH due to ONB to our knowledge (Table 2). The mean age of patients was 41.5. Among described patients were 22 females and 11 males. In 15 cases ADH secretion by the tumor was proven by assay of tumor tissue, whereas in 1 case immunostaining for ADH was negative [45]. There was no information about evidence of ADH secretion by the tumor in the other cases. Three SIADH-associated ONBs were primary sellar neuroblastomas. Interestingly, they represent approximately 27% of all primary sellar neuroblastomas reported in the literature. These ONBs are thought to originate from the ganglion of Lacy that grows between the olfactory fossa and the telencephalic vesicle [46]. There is also a distinctive case of SIADH in a patient with sinonasal teratocarcinoma, which was composed of ONB areas (90% of tumor) and mature craniopharyngioma (10% of tumor). Immunostaining for ADH was positive only in the ONB cells [47]. Besides paraneoplastic, there is also one case of SIADH in advanced ONB induced by cisplatin (CDDP) [48]. A similar situation was also reported in some other cancer patients after CDDP administration [49].

Among all cases, in 26 (75%) after treatment SIADH resolution was recorded, 4 (11.5%) patients died, in 2 (5%) SIADH persisted, and in 1 reset of osmostat (left-shift set point of osmolality) occurred.

Senchak *et al.* described a female patient with ectopic ONB which arose from the middle nasal cavity [50]. She had a 3-year history of hyponatremia prior to ONB diagnosis, which was diagnosed as SIADH and treated by demeclocycline. Furthermore, she became pregnant shortly after ONB discovery. Sodium level and plasma osmolality decreased normally in early pregnancy due to the altered threshold for ADH release and for thirst [51], so there was a risk of overlap between this mechanism and SIADH. To avoid the risk of severe hyponatremia, endoscopic total resection of the neoplasm was performed. After surgery her sodium level and osmolality normalized. She also had an uncomplicated delivery of her pregnancy. Interestingly, in another case reported by Renneboog, hyponatremia associated with ONB normalized during pregnancy and reoccurred after delivery [52]. A possible explanation may be the action of placental peptidases, which are capable of inactivating ADH [53].

Olfactory neuroblastoma is a malignancy with a long natural history due to slow progression. Nevertheless, local recurrences occur in 30% of patients, cervical node metastases in 23%, and distant metastases in 8% of cases. Recurrence or progression even > 10 years after initial presentation are reported [8]. In one case, incidental diagnosis of hyponatremia due to SIADH with a lack of other symptoms led to the finding of ONB recurrence 16 years after primary tumor resection [54]. Interestingly, SIADH did not accompany the primary tumor. On the other hand, Myers *et al.* reported an ADH-secreting primary ONB, which relapsed in the lymph node, but without SIADH reappearance, which can imply that recurrent tumor cells probably lost the ability of ADH production [55].

Another interesting case of SIADH secondary to ONB was presented by Muller *et al.* [56]. A 47-year-old man was admitted to a psychiatric hospital because of a first major depressive episode. He also had a history of hyponatremia due to SIADH of unknown origin. Major depression may be associated with numerous endocrine disturbances such as CS, Addison's disease, hyperthyroidism, hypothyroidism, hyperprolactinemia and also SIADH [57]. ADH when over-expressed and over-released may contribute to hyper-anxiety and depression-like behaviors, because ADH belongs to the neuropeptide system critically involved in higher brain functions [58]. After admission the patient underwent a combined dexamethasone-CRH stimulation test and neither corticotropin nor cortisol plasma levels have increased. Heuser *et al.* showed that psychiatric patients, regardless of diagnostic classification, release more cortisol and ACTH after this test in comparison with controls [59]. This hyperactivity results from increased central production of CRH and desensitization of the glucocorticoid receptor binding system in the hippocampus, which is involved in feedback inhibition of hypothalamic-pituitary-adrenocortical axis activity [60]. Corticotropin-releasing hormone and ADH are known for being the most important stimulants of ACTH secretion. Several studies have shown that the ACTH response to both CRH and ADH undergoes desensitization [61], especially when there is a chronically elevated level of CRH/ADH as in this case of SIADH. Psychiatric symptoms such as major depression, anxiety, hypomania, psychosis and mania may be part of CS clinical manifestations [62]. Inagaki presented a case of ONB relapse manifesting with anxiety, irritability, insomnia, psychomotor excitement and then depressed mood and suicidal ideation. The further investigation revealed CS and treatment with metyrapone was started. The patient's cortisol levels and ACTH levels immediately became normal and psychiatric manifestations resolved. Depression, decreased libido, increased irritability, mood swings, insomnia, and short attention span were also noted in Hodish's patient with EAS associated with ONB [13]. Moreover, besides PNS, in ONB depression and other psychiatric symptoms may also be signs of frontal lobe dysfunction [63, 64].

Recurrent hyponatremia after an ADH-secreting tumor resection have been proposed as a potential marker for persistent disease or tumor recurrence. Nevertheless, Perry *et al.* reported reset osmostat after resection of ADH-secreting ONB, which led to recurrent hyponatremia. Reset

Table 2. Case reports of olfactory neuroblastoma associated with syndrome of inappropriate ADH secretion (SIADH)

Study	Age	Sex	Treatment	Treatment at recurrence	SIADH post Tx/Outcome
Bouche <i>et al.</i> [44]	34	male	surgery	–	resolved
Pope <i>et al.</i> [80]	56	female	surgery + radiotherapy	–	resolved
Singh <i>et al.</i> [86]	17	female	cobalt therapy	–	DDD
Srigley <i>et al.</i> [87]	33	female	surgery + radiotherapy and chemotherapy	–	resolved
Cullen <i>et al.</i> [88]	26	female	surgery + radiotherapy	–	resolved
Osterman <i>et al.</i> [89]	28	male	surgery + radiotherapy	–	resolved
Myers <i>et al.</i> [55]	79	female	conservative treatment	–	DDD
Al Ahwal <i>et al.</i> [45]	27	male	surgery	radiotherapy	resolved
Boursier [69] Bernard [68]	22	male	surgery	–	resolved
Muller <i>et al.</i> [56]	47	male	surgery	–	resolved normalization of psychiatric symptoms
Kleinschmidt <i>et al.</i> [47]	59	male	surgery	surgery	DDD
Miura <i>et al.</i> [70]	56	male	surgery + radiotherapy and chemotherapy	–	maturation to ganglioneuroma after chemotherapy DDD
Freeman <i>et al.</i> [71]	51	female	surgery	–	resolved
	42	female	surgery	–	resolved
Plasencia <i>et al.</i> [54]	34	female	surgery + radiotherapy	surgery + radiotherapy	resolved
Maeda <i>et al.</i> [72]	61	male	radiotherapy	radiotherapy	resolved
Perry <i>et al.</i> [73]	56	female	surgery	–	reset osmostat
Senchak <i>et al.</i> [50]	28	female	surgery	–	resolved
Gray <i>et al.</i> [66]	29	male	surgery + chemotherapy + radiotherapy	–	resolved
	25	female	surgery + radiotherapy	–	resolved
	32	female	surgery + radiotherapy	–	resolved
Iliades <i>et al.</i> [74]	57	female	surgery + radiotherapy	–	resolved
Verbalis <i>et al.</i> [75]	40	female	surgery	–	resolved
Yang <i>et al.</i> [76]	25	female	chemotherapy + radiotherapy	–	resolved
Cho <i>et al.</i> [77]	62	male	chemotherapy	–	resolved
Nabili <i>et al.</i> [78]	NI	female	surgery	NI	resolved; BP normalization
Dupuy <i>et al.</i> [79]	44	female	surgery	–	PRL normalization, SIADH
Schmalisch <i>et al.</i> [46]	43	female	surgery + radiotherapy	–	PRL normalization, SIADH
Radotra <i>et al.</i> [81]	29	male	surgery + radiotherapy	–	resolved
Hoorn <i>et al.</i> [82]	29	female	endonasal ethmoidectomy	–	resolved
Wade <i>et al.</i> [83]	59	female	surgery	chemotherapy	resolved
Renneboog [52]	28	female	surgery + radiotherapy	–	resolved
Garcia Vincente [84]	NI	NI	NI	–	NI
Le Guillou <i>et al.</i> [85]	60	female	surgery	–	resolved
Gabbay <i>et al.</i> [67]	50	male	surgery	–	resolved

DDD – death due to disease; NI – no information; Tx – treatment

osmostat is an altered pattern of ADH secretion in which the threshold for ADH secretion is moved downward. Hyponatremia in these patients will be limited to a value close to the new osmotic set point [38]. A water load test was used in this case to differentiate reset osmostat from

unregulated ADH secretion, which may occur with tumor relapse. With this procedure, a fasting is given specific quantities of water, then the amount of urine produced and the changes in urine and blood osmolality and ADH level are monitored over time [65].

Plasencia *et al.* pointed out that most cases of SIADH from other etiologies are relatively mild, and hyponatremia is generally of little clinical significance, while severe hyponatremia has been described in relation to ONB [54]. Many cases of ONB inducing subclinical SIADH probably have passed unnoticed, and the general number of ADH-secreting ONB may be significantly underestimated. In one retrospective analysis of 21 patients, the prevalence of SIADH was 14% [66]. In 18 cases hyponatremia occurred parallel to ONB diagnosis, whereas in 17 SIADH preceded ONB. In some cases Gabbay *et al.* emphasized that the time interval between the onset of SIADH and the diagnosis of ONB is exceptionally long in this neoplasm [67]. This reflects low awareness of physicians in this area.

Catecholamine secretion

Symptomatic catecholamine secretion by tumors is a rarity. The majority of these tumors are pheochromocytomas and paragangliomas. Pheochromocytomas and sympathetic paragangliomas usually release norepinephrine and/or epinephrine, while 23% of parasympathetic paraganglia-derived tumors secrete only dopamine [90]. As far as head and neck tumors are concerned, approximately 20% of head and neck paragangliomas also produce significant amounts of catecholamines [91]. Main signs and symptoms include paroxysmal or sustained hypertension, severe headaches, palpitations and sweating resulting from hormone excess. Less common are fatigue, nausea, weight loss, constipation, flushing, and fever [92].

Neuroblastomas, pediatric tumors of the sympathetic nervous system, are also associated with catecholamine secretion. Expression of tyrosine hydroxylase could be used diagnostically for the detection of residual NB cells. Conversely, ONBs do not usually secrete catecholamines, and tyrosine hydroxylase is not generally expressed in these tumors [93]. Nevertheless, there are 5 cases of catecholamine-secreting ONBs to our knowledge. Three of them were clinically inactive and catecholamine production was revealed by immunohistochemical and molecular analysis [94–96].

Nabili *et al.* reported a unique case of tumor which secreted both ADH and catecholamines. Patient symptoms included hypernatremia and hypertension. Laboratory studies showed increased blood levels of ADH and normetanephrine and elevated urine metanephrine. Mild 123I-metaiodobenzylguanidine (123I-MIBG) uptake in the right nasal region suggested a catecholamine-secreting tumor. Perioperative treatment with α -blockers, phenoxybenzamine, and phentolamine was applied to prevent intraoperative hypertension. After surgery there were no signs of SIADH, and urine catecholamine levels were markedly decreased. The progressive decrease in catecholamine levels after treatment suggests that catecholamine levels may serve as useful markers for residual disease or recurrence.

Intraoperative unpredictable paroxysmal release of catecholamines can result in catastrophic cardiovascular complications in a previously undiagnosed patient [97]. An intraoperative hypertensive crisis during the first of

two planned stages of ONB surgery in a 56-year-old man was reported by Salmasi *et al.* [98]. Further investigation revealed increased levels of blood and urinary catecholamines. After the second stage of surgery, immunohistochemical studies of tumor tissue revealed that tumor cells were positive for tyrosine hydroxylase. Catecholamine production should be considered in the case of unexpected extreme hypertension during surgical resection of ONB.

Hypercalcemia

Hypercalcemia affects up to 10 to 30% of cancer patients, most frequently those with breast and lung cancer and myeloma [99]. Hypercalcemia is a common complication in many advanced cancers and has a poor prognosis due to the fact that usually it is associated with disseminated disease. Different humoral factors that are released by tumor cells, either locally or systematically, can affect calcium level regulatory systems. The main humoral factor associated with cancer-related hypercalcemia is PTHrP, which is produced by many solid tumors. PTHrP secretion by tumor accounts for 80% of HHM cases [100]. Less common humoral factors secreted by tumors are vitamin D and PTH. Osteolytic activity at sites of skeletal metastases account for 20% of cases [11].

Sharma *et al.* presented the only known case of hypercalcemia as a complication of ONB. The patient was a 52-year-old male smoker with ONB at Kadish stage C, who despite metastatic disease had maintained a good performance status and quality of life. He was treated with chemotherapy and radiotherapy. Surgery of the tumor was not performed because the patient declined. Six months after the last course of radiotherapy, symptomatic hypercalcemia occurred (corrected serum calcium 12.7 mg/dl; normal 9–10.3 mg/dl). Treatment included forced saline diuresis, subcutaneous calcitonin, and intravenous gallium nitrate. Despite a backache perceived by the patient, there were no spinal metastases in the administered MRI. Hypercalcemia had recurred for several months and proper treatment was performed. At the time of the next admission, the serum PTH was 5 pg/ml (normal 10–60 pg/dl) despite severe symptomatic hypercalcemia that did not respond to aggressive treatment, which was the cause of death.

Hypercalcemia, which is resistant to treatment can be induced by ectopic PTH secretion or primary hyperparathyroidism, but low levels of PTH in this case excluded that. Negative whole spine MRI makes widespread bone metastases unlikely. Even though Sharma *et al.* did not measure the level of PTHrP, the HHM secondary to PTHrP secretion by the primary tumor or by metastases is a likely cause of hypercalcemia in this case. HHM may be an important adverse prognostic indicator, as in other malignancies, having serious implications for diagnosis, prognosis, and treatment decisions in ONB.

Hyperprolactinemia

Hyperprolactinemia in cancer patients is often associated with ectopic prolactin (PRL) production by tumors. Primary sellar neuroblastomas are the only known forms of ONBs in which hyperprolactinemia were reported. How-

Table 3. Case reports of neurological paraneoplastic syndromes in olfactory neuroblastoma

Study	Sex	Age	Clinical manifestation/ course	Onconeural antibodies	Neuroimaging	Treatment	Outcome
Van Dienst <i>et al.</i> [106]	female	51	at admission: opsoclonus, vertigo, vomiting, severe ataxia of the four limbs, dysarthria, sporadic myoclonic muscle jerks; two postoperative relapses	anti-Hu, anti-Yo and anti-Ri – negative	a tumor of the nasal septum and the ethmoidal sinuses	methylprednisolone; surgery; chemotherapy and radiotherapy	patient able to walk about with a walking aid
Maeda <i>et al.</i> [109]	male	65	7 years before admission olfactory neuroepithelioma; at admission: gait instability; dysmetria marked in both legs and poor heel-shin test; downbeat nystagmus; tandem gait was impossible	anti-Hu – positive; anti-Yo, Ri, CV2, Tr, Ma, amphiphysin, glutamic acid decarboxylase – negative. Immunohistochemistry with anti-HuD antibody – part of the tumor expressed Hu protein	bilateral leukoaraiosis at bilateral frontal lobes; slightly atrophic cerebellum	NI	4 years after discharge, the cerebellar ataxia did not worsen further

NI – no information

ever, it is thought to be a consequence of the stalk effect, not ectopic PRL production [46, 79, 101]. Nevertheless, Skinner presented an interesting alternative hypothesis in which he stated that suprasellar tumors secrete a specific pars tuberalis factor, like preprotachykinin A derived tachykinins, substance P and/or neurokinin A, that stimulates PRL secretion [102]. Therefore, hyperprolactinemia in these tumors would have features of PNS.

Neurological paraneoplastic syndromes

Opsoclonus-myoclonus-ataxia (OMA) is a rare autoimmune condition characterized by disinhibition of the fastigial nucleus of the cerebellum. Symptoms includes involuntary multidirectional saccades with horizontal, vertical, and torsional components and brief multifocal myoclonic muscle jerks usually accompanied by cerebellar dysfunction with dysarthria and ataxia, hence the name “dancing eyes, dancing feet syndrome” [103]. Neuronal damage is probably caused by T-cell dependent reactions. Nevertheless, OMA and some other neurological PNS are known to be associated with presence of special antibodies, known as onconeural antibodies (anti-Hu, Yo, Ri, CRMP5, Ma, amphiphysin), which are directed against intracellular antigens expressed by the tumor. Although they have low pathogenic significance, they are useful diagnostic markers of paraneoplastic etiology [104]. However, the lack of detectable onconeural antibodies does not exclude the PNS diagnosis. Half of all cases occur in children with neuroblastoma, frequently showing diffuse and extensive lymphocytic infiltration with lymphoid follicles [105]. In adults there are multiple etiologies: besides paraneoplastic (most frequently due to SCLC and breast cancer), also post-infectious, celiac disease, pregnancy, post-vaccination and idiopathic [106]. There is one reported case of OMA due to ONB. In contrast to endocrine PNS, paraneoplastic neurologic syndromes are detected before cancer is diagnosed in 80% of cases, and this was the case in the single reported ONB patient [11].

In this case, a 51-year-old woman presented subacute onset of OMA. Clinical findings are presented in Table 2. Two weeks prior to admission, the patient underwent a bi-

opsy of a polypoid lesion in the right nasal cavity. Pathology revealed a Hyams’ grade 4 ONB with diffuse and extensive lymphocytic infiltration, but without lymphoid follicles.

Conversely to the monophasic course observed in idiopathic OMA, the relapsing-remitting profile is typical for paraneoplastic OMA, as seen in this case [107].

Pediatric neuroblastoma patients with OMA show a less aggressive course of the disease. These tumors also have a tendency to involute spontaneously or mature, and in 90% no metastases are found [105]. Due to these facts, neuroblastic tumors in patients with OMA are associated with a good prognosis. However, in adults the majority of patients with paraneoplastic OMA make only a partial recovery, and some even die due to severe encephalopathy and coma development [107]. In the presented ONB patient with OMA, skin metastases were found, but after proper treatment her state improved and no other lesions were reported.

Olfactory neuroepithelioma is classified as a variant of ONB [108]. Maeda *et al.* reported a case of a 65-year-old man with recurrence of olfactory neuroepithelioma in the parotid gland, with parallel onset of neurological manifestation (Table 3) [109]. The recurrence might have enhanced the immune response. Despite resection of the recurrent tumor, the cerebellar ataxia worsened for several months after surgery. However, it did not progress thereafter.

In patients with neurological symptoms and Hu antibody, olfactory neuroepithelioma should be considered when a neoplasm is not found at common sites such as the lung or breast.

Conclusions

Amongst all PNS that may occur in ONB, SIADH was the most frequently reported. Physicians should be aware that idiopathic hyponatremia may be caused by ONB. Similarly, in long lasting CS without an obvious cause, one should consider “looking at the sinus”. However, caution is strongly recommended when analyzing IPSS, HDDST and CRH stimulation test findings due to the high prevalence of false results. Both SIADH and EAS are generally associated with good prognosis.

Other PNS, especially neurological, are extremely rare in these tumors. Opsoclonus-myooclonus-ataxia is a relatively common PNS in pediatric neuroblastoma and in one case was associated with ONB. This suggests that occasionally ONB may behave like a pediatric neuroblastoma.

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