Olfactory neuroblastoma (esthesioneuroblastoma) presenting as ectopic ACTH syndrome: always follow your nose

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Summary

ACTH-dependent hypercortisolism is caused by an ectopic ACTH syndrome (EAS) in 20% of cases. We report a rare cause of EAS in a 41-year-old woman, presenting with clinical features of Cushing's syndrome which developed over several months. Biochemical tests revealed hypokalemic metabolic alkalosis and high morning cortisol and ACTH levels. Further testing, including 24-hour urine analysis, late-night saliva and low-dose dexamethasone suppression test, confirmed hypercortisolism. An MRI of the pituitary gland was normal. Inferior petrosal sinus sampling (IPSS) revealed inconsistent results, with a raised basal gradient but no rise after CRH stimulation. Additional PET-CT showed intense metabolic activity in the left nasal vault. Biopsy of this lesion revealed an unsuspected cause of Cushing's syndrome: an olfactory neuroblastoma (ONB) with positive immunostaining for ACTH. Our patient underwent transnasal resection of the tumour mass, followed by adjuvant radiotherapy. Normalisation of cortisol and ACTH levels was seen immediately after surgery. Hydrocortisone substitution was started to prevent withdrawal symptoms. As the hypothalamic-pituitary-axis slowly recovered, daily hydrocortisone doses were tapered and stopped 4 months after surgery. Clinical Cushing's stigmata improved gradually.

Learning points:

- Ectopic ACTH syndrome can originate from tumours outside the thoracoabdominal region, like the sinonasal cavity.
- The diagnostic accuracy of IPSS is not 100%: both false positives and false negatives may occur and might be due to a sinonasal tumour with ectopic ACTH secretion.
- Olfactory neuroblastoma (syn. esthesioneuroblastoma), named because of its sensory (olfactory) and neuroectodermal origin in the upper nasal cavity, is a rare malignant neoplasm. It should not be confused with neuroblastoma, a tumour of the sympathetic nervous system typically occurring in children.
- If one criticises MRI of the pituitary gland because of ACTH-dependent hypercortisolism, one should take a close look at the sinonasal field as well.

Background

Ectopic ACTH syndrome (EAS) accounts for 10–18% of all types of Cushing's syndrome. EAS is most frequently caused by a small-cell lung carcinoma ($\pm 50\%$). Olfactory

neuroblastoma (ONB) is an extremely rare cause of EAS, of which only 21 cases have been reported. When suspecting an ectopic cause of ACTH hypersecretion, it is important to look beyond the thoracoabdominal region and also consider the sinonasal cavity. This is especially true in

case of inconsistent IPSS results, due to the possibility of false positives or false negatives.

Case presentation

A 41-year-old Caucasian woman with prior history of bariatric surgery, IVF-induced pregnancy and post-partum thyroiditis presented with a Cushingoid appearance. Her symptoms developed over 5 months and included rounding of the face, alopecia of the scalp, hirsutism on the upper lip, easy bruisability, amenorrhea and proximal muscle weakness of the lower limbs. She mentioned a pressing headache and slight deterioration of vision. Clinical examination revealed a rounded face, centripetal obesity, proximal muscle atrophy, thinned scalp hair, hyperpigmentation in sun-exposed neck region, ecchymosis and arterial hypertension (Fig. 1).

Investigation

Multiple laboratory tests were performed, as depicted in Table 1. Blood analysis showed elevated morning cortisol and ACTH levels, hypokalemic metabolic alkalosis and hypernatraemia. Cushing's syndrome was diagnosed with elevated 24-hour urinary cortisol excretion, elevated late-night salivary cortisol and no suppression of morning cortisol after low-dose dexamethasone suppression test. We noted high ACTH and cortisol values at midnight and loss of circadian rhythm as a sign of ACTH dependency (Table 2).

MRI of the pituitary gland showed no pituitary adenoma. Inferior petrosal sinus sampling (IPSS) was performed with use of contrast enhancement to ensure correct catheter placement. Absolute ACTH values during IPSS are displayed in Table 3. Central-to-peripheral ACTH gradient was 2.8: clearly above the cut-off of 2.0 and therefore compatible with Cushing's disease. However, we did not measure the expected rise in ACTH gradient after CRH stimulation, with a central-to-peripheral gradient below 3.0 (Table 3). Additional PET-CT showed intense metabolic activity in the left anterior ethmoidal sinus and left upper nasal turbinate, extending to the middle and lower left nasal cavity (Fig. 2A, B and C). Reassessment of initial MRI of pituitary gland confirmed the presence of a sinonasal mass.

Anatomopathological investigation of this polypoid lesion showed typical cellular nests of small round blue cells with a high nuclear-to-cytoplasmic ratio, rare nucleoli and a nuclear chromatin pattern typical of neuro-endocrine-like tumours (Fig. 3A). Immunohistochemical staining showed positivity for multiple neuro-endocrine

Figure 1

Clinical examination revealed a rounded face (B). Picture A was 2 years ago and was added for comparison. Several months after treatment (C), Cushingoid stigmata clearly improved.

markers, such as CD56, synaptophysin, chromogranin A and INSM1 (Fig. 3B). S100 staining highlighted the support cells surrounding the tumour nests, also known as sustentacular (Schwann) cells (Fig. 3C), needed to differentiate ONB from melanoma. Staining for pancytokeratine AE1/AE3 marker was negative, ruling out a neuro-endocrine tumour type carcinoid or neuro-endocrine carcinoma. Finally, cytoplasm cross-reacted with a mouse ACTH monoclonal antibody, proving ACTH overexpression of the olfactory neuroblastoma (Fig. 3D).

We took a CT scan with thin slices in the coronal plane for better evaluation of the lamina cribrosa. It confirmed a large soft tissue mass in the left nasal vault extending to the lamina cribrosa on one side and to the middle and lower nasal turbinate on the other side. There was no evidence of further protrusion into the anterior cranial fossa nor the orbits (Fig. 2D).

Treatment

Our patient underwent transnasal endoscopic resection of the tumour mass (Fig. 4). The entire left middle concha was tumourally transformed and removed as far as the lamina cribrosa, which also showed signs of tumoral invasion. The exposed dura mater and nasal

Table 1 Overview of laboratory results.

	Result	Reference value
Blood		
Sodium (mmol/L)	149	135–145
Potassium (mmol/L)	2.6	3.5–5.1
Chloride (mmol/L)	108	98–107
Bicarbonate (mmol/L)	34	21–32
Urea (mg/dL)	26	15–39
Creatinine (mg/dL)	0.73	0.55–1.02
CRP (mg/L)	13.9	<3.0
Cortisol (µg/dL)	27.7	10–20
ACTH (pg/mL)	66.1	10–60
Cortisol after LDST	9.1	<5
24-hour urine		
Volume (mL)	950	
Cortisol (µg/dL)	101.4	
Cortisol (µg/24h)	963	21–292
Creatinine (mg/dL)	71	15–278
Creatinine (mg/24h)	956	800–2000
Potassium (mmol/24 h)	17	25–125
Saliva		
Cortisol (µg/dL)	0.437	<0.1

ACTH, adrenocorticotrophic hormone; CRP, C-reactive protein; LDST, low-dose dexamethasone suppression test.

septum showed no signs of tumour damage. Adjacent sinuses were opened for aspiration of retro-obstructive mucus. Anatomopathological investigation confirmed our previous diagnosis. Totality of resection could not be proven by histology, only macroscopically. Postoperative values of cortisol and ACTH were undetectable (respectively <5 pg/mL and 0.8 µg/dL), suggestive of successful resection.

The tumour was categorised as Kadish stage A (with confinement to the nasal vault) or B (considering the uncertainty of paranasal sinus invasion). We opted for adjuvant radiotherapy (30 sessions of 2 grey; by Volumetric Modulated Arc Therapy (VMAT) technique) given the equivocal Kadish stage, relative high risk of ONB recurrence, our patient's young age and minimal side effects to be expected.

Outcome and follow-up

Postoperative cortisol and ACTH levels were undetectable. Hydrocortisone substitution was started at a total daily

dose of 30mg distributed in three gifts to prevent withdrawal. As the hypothalamic–pituitary–adrenal axis slowly recovered, daily hydrocortisone dose was tapered and finally stopped 4 months after surgery. Clinical Cushing stigmata slowly improved. Morning serum cortisol and ACTH levels were monitored every 2–3 months. After radiotherapy is finished, control MRI of the sinonasal cavities and nasal endoscopy will be performed.

Discussion

Difficulties in diagnosing EAS

After establishing Cushing's syndrome, several tests are possible to distinguish Cushing's disease from EAS. The more invasive IPSS test is considered to be the most reliable one (1, 2, 3, 4). IPSS is recommended in all patients with ACTH-dependent hypercortisolism with (1) no lesion or a lesion <6 mm on MRI and with (2) mixed or negative response on CRH stimulation or dexamethasone suppression tests (1, 5). A baseline central-to-peripheral gradient above two or a post-CRH stimulation central-to-peripheral gradient above three indicates pituitary Cushing's ('positive gradient'), whereas the absence of a gradient suggests ectopic Cushing's ('negative gradient'). Initial studies reported a near-perfect sensitivity and specificity of IPSS (3). However, subsequent studies showed that diagnostic accuracy is not always 100% (1, 2, 6). False negatives occur in 10–15% of patients. There are several explanations for such false-negative results. First, sampling errors occur due to technical difficulty of the procedure and/or due to anatomical variations of the petrosal sinus venous system. Correct catheter placement should be verified by using contrast-enhanced fluoroscopy imaging or measuring other pituitary hormones such as prolactin (1). Second, patients must be in a hypercortisolemic state at the time of the IPSS procedure, warranting suppression of endogenous pituitary corticotrophs. Suppression of endogenous ACTH or CRH release ensures that any measurable ACTH in the obtained samples is secreted by the neoplasm (3). This means that any medical treatment to control hypercortisolism must be stopped well in advance (1, 3). Thirdly, due to variable

Table 2 Cortisol day curve (blood analysis).

	24/10/2018 08:00	24/10/2018 12:00	24/10/2018 16:00	24/10/2018 20:00	25/10/2018 00:00	25/10/2018 04:00
Cortisol (µg/dL)	17.9	14.2	30.2	15.9	22.6	15.7
ACTH (pg/mL)	19.8	13.1	41.1	28.3	34.6	16.4

ACTH, adrenocorticotrophic hormone.

Table 3 Absolute ACTH values and ACTH IPS:P ratios during IPSS.

ACTH (pg/mL)	Basal	3 min post CRH	10 min post CRH
Peripheral	11	23	26
Left IPSS	27	32	29
Right IPSS	31	32	31
Highest IPS:P ratio	2.8	1.4	1.2

ACTH, adrenocorticotrophic hormone; IPS:P ratio, inferior petrosal sinus to peripheral ratio; IPSS, inferior petrosal sinus sampling.

ACTH secretion, a positive central-to-peripheral gradient may not be reached at time of IPSS. False-positive results are less frequently seen. One explanation is tumour localisation adjacent to the upstream of pituitary venous drainage, as in our case. Olfactory neuroblastoma and sphenoidal sinus ectopic pituitary adenoma are known for causing such false positive gradients. Another possibility is sampling performed by chance in a eucortisolemic state, that is, by a tumour with intermittent hypercortisolism.

This theory implies rapid recovery of the HPA axis, which is in contrast to the typically slow recovery of the HPA axis seen in daily practice (2).

Olfactory neuroblastoma

Olfactory neuroblastoma (syn. esthesioneuroblastoma) is a rare malignant neuroectodermal nasal tumour, representing about 3% of all sinonasal malignancies (7, 8). It should not be confused with neuroblastoma, a tumour of the sympathetic nervous system typically occurring in children. The tumour ONB is thought to arise from specialised sensory neuroepithelial (neuroectodermal) olfactory cells, which can be found in the upper nasal cavity. This olfactory epithelium consists of three cell types: basal cells, olfactory neurosensory cells and supporting sustentacular cells (7). All three cell types were histologically identified in our case. Typical clinical features include unilateral nasal congestion,

Figure 2

PET-CT scan showed intense metabolic activity in the left anterior ethmoidal sinus and left upper nasal turbinate, extending to the middle and lower left nasal cavity. Axial (A), coronal (B) and sagittal (C) view are represented. CT scan confirmed a soft tissue mass at the nasal vault extending to the lamina cribrosa. Coronal (D) view is represented.

Figure 3

Anatomopathological investigation showed a pattern typical of neuro-endocrine-like tumours (A). Immunohistochemical staining showed positivity for synaptophysin (B). S100 staining highlighted the support cells surrounding the tumour nests, also known as sustentacular (Schwann) cells (C). Cytoplasm cross-reacted with monoclonal mouse ACTH antibody, proving ACTH overexpression of the olfactory neuroblastoma (D).

recurrent epistaxis, sinusitis, headache and anosmia (7, 8). ONB may be associated with endocrine and neurologic paraneoplastic syndromes. SIADH (syndrome of inappropriate ADH secretion) is most frequently reported (9). ONB presenting with EAS is extremely rare. To our knowledge, only 21 cases have been reported. In 8 of these 21 cases, Cushing's syndrome was the initial presentation of the underlying tumour. For example in Yu *et al.* a 55-year-old male presented with muscle weakness, truncal obesity and hypokalemic metabolic alkalosis (10). In Familiar *et al.* a 31-year-old male presented with persistent hypertension since 2 years and a Cushingoid phenotype (11). A more rapid development of symptoms, hypokalaemia and metabolic alkalosis tend to be typical features of EAS. Of the 21 patients with ONB and EAS, hypokalaemia was mentioned in 14 cases (67%) and metabolic alkalosis in 9 cases (43%) (9, 10, 11, 12).

Multiple staging systems were proposed, but the Kadish staging system is most commonly used. Patients are categorised as (A) tumour limited to the nasal cavity only, (B) involvement of the paranasal sinuses, (C) extension beyond the nose and paranasal sinuses and (D) presence of cervical lymph nodes or distant metastases at time of diagnosis (7, 8, 9).

Given the rarity of ONB there is no true standard care for treatment, but the mainstay of treatment is surgery (8).

Transnasal endoscopic resection is minimally invasive and is preferred over the traditional, more invasive, open craniotomy with facial incisions. More advanced tumour stages can be a relative contraindication for transnasal approach (8). Adjuvant radiotherapy is administered to minimise the risk of local recurrence, especially in well to moderately differentiated tumours. Chemotherapy is used in poorly differentiated, advanced, unresectable, disseminated or recurrent disease (7, 8). There is no standard chemotherapy regimen, but platinum-based regimens combined with etoposide are most commonly used (8).

Reported 5-year survival rates range from 57 to 93% (7, 8). Prognosis of ONB depends on age at diagnosis, Kadish stage, lymph node status and treatment modality (13). Improved survival was observed with multimodality treatment (both surgery and radiotherapy, median 5-year survival rate of 65%) as opposed to radiotherapy alone (median 5-year survival rate of 45%) ($P < 0.002$) (13). In spite of high survival rates, recurrence is very common: about 30% (range 15–70%) of patients develop recurrent disease after initial management (7). Recurrence is mostly locoregional, but up to 25% of patients develop cervical lymph node metastasis and up to 10% distant metastasis, typically in lungs and bones (7, 8).

Figure 4

Endoscopic visualisation of the tumour mass in the left nasal cavity. The entire left middle concha was tumourally transformed.

Conclusion

Olfactory neuroblastoma is an extremely rare cause of EAS. Inconsistent IPSS results might be caused by an ACTH-producing tumour in the sinonasal region, due to its anatomical proximity to the venous drainage of the pituitary gland. In case of EAS, we advise to look beyond the thoracoabdominal region and also consider the sinonasal cavity.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Author contribution statement

K D and V W both equally contributed to gathering clinical data, writing this article and conducting literature research. N V D and PC managed the case and reviewed the manuscript.

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