A 41-year-old woman presented with a puffy face since five months. She experienced alopecia, hirsutism, easy bruising, amenorrhea and proximal muscle weakness. Clinical examination revealed a moonface, centripetal obesity, proximal muscle atrophy, thinned scalp hair, hyperpigmentation in sun-exposed neck region, ecchymosis and arterial hypertension grade 1. Blood analysis showed elevated morning cortisol, elevated morning ACTH of 66.1 pg/ml (normal 10-60), hypokalemic metabolic alkalosis (potassium 2.6 mmol/l, bicarbonate 34 mmol/l) and hypernatremia (149 mmol/l). Cushing’s syndrome was diagnosed with elevated 24-hours urinary cortisol excretion of 963 μg/24 hours (normal 21-292) and elevated late-night salivary cortisol of 0.437 μg/dl (normal <0.107). Loss of circadian rhythm and high ACTH and cortisol values at midnight confirmed ACTH dependency.

No adenoma could be visualised on MRI of the pituitary gland. Inferior petrosal sinus sampling (IPSS) displayed a central-to-peripheral ACTH gradient of 2.8: clearly above the cut-off of 2.0. Surprisingly, we did not observe the expected rise in ACTH gradient after CRH-stimulation, with a gradient below 3.0 (1.4 after 5 minutes and 1.2 after 10 minutes).

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 (Figure 1). Biopsy of this polypoid lesion revealed an olfactory neuroblastoma (ONB) with positive immunostaining for ACTH (Figure 2).

Our patient underwent endoscopic resection of the tumour as far as the lamina cribrosa, including resection of the entire middle turbinate. The exposed dura mater and the nasal septum showed no signs of tumour invasion (Figure 3-4). Postoperative values of cortisol and ACTH were undetectable, suggestive of successful resection. Anatomopathological analysis confirmed our previous diagnosis.

Olfactory neuroblastoma (syn. esthesioneuroblastoma) is a rare neoplasm originating from neuroectodermal olfactory cells situated in the upper nasal cavity, representing about 3% of all sinonasal malignancies. Typical clinical features include unilateral nasal congestion, recurrent epistaxis, sinusitis, headache and anosmia (1, 2). ONB presenting with ectopic ACTH syndrome (EAS) is extremely rare. To our knowledge, only 21 cases have been published. IPSS is considered to be the most reliable test to distinguish Cushing’s disease from ectopic ACTH secretion, however, subsequent studies showed that diagnostic accuracy is not always 100% (3, 4). False negatives occur in 10-15% of patients. First, sampling errors occur due to technical difficulty of the procedure or anatomical variations of the petrosal sinus venous system (3). Second, patients must be in a hypercortisolemic state at the time of the IPSS procedure, warranting suppression of endogenic pituitary corticotrophs (5). Therefore, medical treatment to control hypercortisolism must be stopped well in advance (3, 5). Thirdly, due to variable 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 localization adjacent to the upstream of pituitary venous drainage, as in our case (4).

Clinicians should be aware that inconsistent IPSS results might be due to an ACTH-producing tumour in the sinonasal region. In case of EAS, especially with inconsistent IPSS results, one should always follow one’s nose and look at the sinonasal region.

**REFERENCES**