CASE REPORT

An unusual manifestation of olfactory neuroblastoma

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SUMMARY

A 62-year-old woman presented with an 11-month history of worsening nasal symptoms of rhinorrhoea, anosmia, nasal congestion and intermittent epistaxis. MRI revealed a large mass in the upper nasal vault. Biopsy of the mass revealed an olfactory neuroblastoma. While waiting resection, she acutely developed severe proximal muscle weakness, lethargy and lower extremity oedema. Blood glucose was elevated, and hypokalaemic metabolic alkalosis was noted. Elevated serum cortisol level of 95.7 µg/dL (8.7–22.4 µg/dL) and markedly elevated 24-hour urinary cortisol level of 6962.3 µg/24 hours (4.0–50.0 µg/24 hours) with concurrent adrenocorticotrophic hormone (ACTH) level of 171 pg/mL (6–58 pg/mL) were suggestive of an ACTH-dependent source of hypercortisolism. A subsequent positive high-dose dexamethasone suppression test was consistent with ectopic ACTH production. She underwent near-total resection of the right nasal mass followed by radiotherapy, resulting in complete resolution of signs and symptoms of cortisol excess.

BACKGROUND

This case illustrates an exceedingly uncommon presentation of olfactory neuroblastoma (ON) and the need for early recognition of the acute presentation of hypercortisolism.

Given the spectrum of clinical presentation, challenges in diagnosis and absence of specific treatment guidelines, it is important to be aware of this

challenging diagnosis. The clinical presentation, diagnostic work-up and management of this rare disease may be unfamiliar to many practising physicians.

CASE PRESENTATION

A 62-year-old woman with a history of hypertension, hyperlipidaemia and obesity was referred for otolaryngology evaluation on account of an 11-month history of progressive rhinorrhoea, anosmia, intermittent epistaxis and right nasal obstruction. MRI (figure 1) revealed a large mass in the upper nasal vault, 6.5 cm×2.5 cm×5 cm in size, filling the right ethmoid sinuses and extending to the orbit with erosion of the right cribriform plate. Biopsy of the mass was consistent with ON grade II. Immunohistochemical stains were positive for synaptophysin and chromogranin A with a Ki-67 proliferative index of <5%.

Neurosurgical evaluation was planned; however, prior to undergoing resection and within 2 months of the biopsy, she presented to the emergency room with lethargy, lower extremity oedema and severe muscle weakness. Physical examination revealed a rounded face, central obesity, violaceous abdominal striae, lower extremity oedema and proximal muscle weakness, consistent with Cushing's syndrome (CS).

INVESTIGATIONS

Investigations (table 1) revealed hypokalaemic metabolic alkalosis with serum potassium of 1.8 mEq/L and bicarbonate of 54 mEq/L. Blood glucose

Figure 1 Sagittal and coronal MRI images. Enhancing 6.5 cm×2.5 cm×5 cm mass (indicated by white arrows) in the right basal frontal lobe extended across the cribriform plate, involved the nasal cavity and ethmoid air cells. There were osseous erosion of the right cribriform plates, thinning of the right lamina papyracea and vasogenic oedema in the right frontal lobe.

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Figure 2 Olfactory neuroblastoma undermining sinonasal mucosa (A; 100 $\times$) and invading sinonasal bone (B; 200 $\times$). (C) Some regions contained organised nests (right) and others showed neurofibrillary elements and occasional crushed cells (left). Tumour cells had a nested architecture, indistinct cell borders, oval nuclei with speckled chromatin and occasional prominent nucleoli (D; 400 $\times$).

was elevated. Further evaluation demonstrated serum cortisol of 95.7 $\mu\text{g/dL}$ (8.7–22.4 $\mu\text{g/dL}$), adrenocorticotropic hormone (ACTH) level of 171 pg/mL (6–58 pg/mL) and 24-hour urinary free cortisol of 6962.3 $\mu\text{g/24 hours}$ (4.0–50.0 $\mu\text{g/24 hours}$). An 8 mg overnight dexamethasone suppression test with unsuppressed cortisol level of 80 $\mu\text{g/dL}$ was consistent with ectopic ACTH secretion.

DIFFERENTIAL DIAGNOSIS

Cushing's disease, ectopic ACTH and ectopic corticotropin-releasing hormone (CRH) syndromes.

TREATMENT

The patient was started on ketoconazole 200 mg two times per day, spironolactone 25 mg two times per day, potassium supplementation and insulin therapy. Otolaryngology and neurosurgery collaborated to perform an endoscopic bilateral maxillary

antroostomy, ethmoidectomy, sphenoidectomy, frontal exploration and craniofacial resection of the right nasal mass. Ketoconazole was discontinued on the day of surgery. Intravenous dexamethasone 4 mg, every 6 hours, was started intraoperatively and continued in the postoperative period. She had an uncomplicated postoperative course. Serum cortisol level prior to discharge and after discontinuing parenteral steroids was 9.1 $\mu\text{g/dL}$. She was discharged on hydrocortisone 20 mg in the morning and 10 mg in the afternoon, for outpatient taper. She was tapered off hydrocortisone over a 3-week period, with demonstration of recovery of normal adrenal function with normal serum cortisol levels after discontinuation of glucocorticoid treatment.

OUTCOME AND FOLLOW-UP

Three months later, she underwent intensity-modulated radiation therapy with 5940 cGy in 33 fractions to address residual tissue. Elective neck radiotherapy was proposed, but she declined. All symptoms related to hypercortisolism resolved within 4 months of surgery. During this period, insulin therapy was no longer needed and discontinued. To assess for recurrence, 24-hour urinary free cortisol levels were periodically checked and remained within normal limits, 2.5 years postsurgery and radiotherapy.

DISCUSSION

This report describes an unusual manifestation of an ON. This patient rapidly developed clinical features of CS, and investigations were suggestive of an ectopic source of ACTH. Surgical removal of the mass, followed by radiotherapy, has led to 2.5 years of biochemical, clinical resolution of CS and disease-free survival. Her response to treatment confirms the diagnosis of the rare ACTH-producing ON.

ON is a rare malignant neoplasm developing from olfactory neuroepithelium and typically located in the superior nasal cavity at the olfactory cleft. It accounts for approximately 2% of all sinonasal tract tumours with an incidence rate of about 0.4 per million population.¹ A review of the Surveillance, Epidemiology, and End Results tumour registry of the epidemiology of ON conducted over a 30-year period (1973–2002) revealed a mean age of 53 years; unimodal distribution in the 5th to 6th decade and slight male preponderance of 55% of cases.² This

Table 1 Preoperative and postoperative laboratory investigations

Laboratory investigation	Preoperative	Postoperative	Reference range
Cortisol post 8 mg overnight dexamethasone test	80		Morning 8.7–22.4 $\mu\text{g/dL}$ Evening <10.0 $\mu\text{g/dL}$
Random cortisol	68.5 (04:00 hours) 95.7 (04:00 hours)	9.1 (06:00 hours)	
ACTH	171		6–58 pg/mL
24-hour urinary free cortisol	6962.3	29	4.0–50.0 $\mu\text{g/24 hours}$
24-hour urinary volume	2100		mL
24-hour urinary creatinine	0.89		0.63–2.50 g/24 hours
Serum sodium	146	140	133–145 mmol/L
Serum potassium	1.8, 2.1, 3.8	3.7	3.3–5.1 mmol/L
Serum chloride	91	110	98–108 mEq/L
Serum bicarbonate	50	28	21–31 mEq/L
Serum blood urea nitrogen	13	8	8–24 mg/dL
Serum creatinine	0.89 g/24 hours	0.54	0.63–2.50 mg/dL
Glomerular filtration rate	>60		>60 mL/min/1.73 m ²
Plasma glucose	181 mg/dL	90	70–99 mg/dL

ACTH, adrenocorticotropic hormone.

tumour can be rarely associated with paraneoplastic syndromes including CS, syndrome of inappropriate antidiuretic hormone secretion, hypercalcaemia, catecholamine secretion and neurological manifestations. To the best of our knowledge, this is the 19th reported case of an ACTH-producing ON, resulting in CS.³

As was the case for this patient, the tumour commonly causes nasal symptoms: predominantly nasal obstruction (unilaterally) and epistaxis. Less common symptoms such as rhinorrhoea, headaches, visual disturbances, lacrimation, headaches and anosmia may also be seen.

The rapid onset of symptoms of CS is a characteristic finding of ectopic ACTH secretion, as was noted in this case, compared with the gradual onset seen with ACTH-producing pituitary adenomas (Cushing's disease).⁴ Widely accepted guidelines for diagnosis of CS recommend initial testing with 24-hour urinary cortisol with creatinine to assess for adequacy of the collection; late night salivary cortisol or overnight dexamethasone suppression test.⁵ Once hypercortisolism is confirmed, subsequent measurement of ACTH is necessary to determine the cause of CS and further stratify as ACTH dependent or independent. This patient had an exceptionally elevated ACTH level of 171 pg/mL (6–58 pg/mL) when serum cortisol was also elevated. This narrows the differential list to three main candidate diagnoses: Cushing's disease, ectopic ACTH and ectopic CRH syndromes. A subsequent high-dose dexamethasone or CRH stimulation test helps to discriminate further; suppression of cortisol post dexamethasone administration is suggestive of pituitary adenoma, while non-suppression points towards an ectopic source. This patient had an elevated cortisol of 80 µg/dL post 8 mg dexamethasone suppression test suggestive of an ectopic source. The ON represented a potential source of ACTH, and the clinical and biochemical resolution of CS after ON resection confirmed the diagnosis. Immunohistochemical staining on the tumour tissue was not performed as it was deemed unremarkable in this setting; up to 40% of pituitary adenomas immunoreactive for ACTH are not associated with signs of hypercortisolism,⁶ suggesting a lack of clinical specificity for CS.

In general, inferior petrosal sinus sampling may be pursued to further evaluate ACTH-dependent CS. It is important to note that the ACTH-producing ON may pose a diagnostic challenge due to the potential false-positive inferior petrosal sinus result. This may occur more commonly with ON due to the adjacent location of the tumour to the ethmoid sinus causing mixing of effluent from ethmoid sinus to the upstream pituitary venous drainage.⁷ False-positive results have also been reported for high-dose dexamethasone suppression and CRH stimulation tests. Non-ectopic pituitary adenomas presenting as nasopharyngeal or polypoid sinonasal masses have been described.⁸ ON with ectopic ACTH secretion historically carries a favourable prognosis, with only two known deaths associated with this disease reported.³

With resection of the mass, there is expected to be sudden withdrawal of hypercortisolism, resulting in adrenal insufficiency. This patient was treated with high-dose glucocorticoids to address oedema from the neurosurgical procedures, but also to treat presumed adrenal insufficiency that occurs after excision of the ACTH-secreting tumour. At the time of excision, the sudden cessation of chronic hypercortisolism in the setting of suppressed hypothalamic–pituitary–adrenal axis may lead to tertiary adrenal insufficiency. To assess if glucocorticoid treatment was necessary, an early morning cortisol level was tested prior to the next dose of dexamethasone. A cortisol level of <10 µg/dL was concerning for adrenal insufficiency, which led to her being discharged on a supraphysiological dose of hydrocortisone, for taper as tolerated.

Pathology revealed a proliferation of neoplastic cells with a lobular architecture infiltrating sinonasal mucosa and invading sinonasal bone (figure 2). Tumour cells had scattered neurofibrillary elements, indistinct cell borders and oval nuclei with speckled chromatin and occasionally prominent nucleoli. Homer Wright pseudorosettes may be seen, particularly in the lower grade ONs, but were not prominent in this case. ONs are graded according to the Hyman's grading system, which is based on cellular architecture and pleomorphism, neurofibrillary matrix and rosettes, mitoses and necrosis.¹ The tumour was graded as Hyman's grade II, due to increased nuclear pleomorphism, increased mitotic activity and less neurofibrillary elements compared with a grade I ON. In contrast, Hyman's grade III and IV ONs have a poorer clinical outcome and histologically would be increasingly anaplastic and poorly differentiated with loss of neurofibrillary elements and lobular architecture.

There are insufficient data regarding optimal management of ON in general. The combined approach of surgery followed by radiation therapy is the most widely used approach and was used for this patient. Adrenolytic medical therapy, ketoconazole in this case, may be employed to optimise the patient while waiting surgery or if there is incomplete resolution of CS symptoms.

This case scenario describes a woman with initial nasal symptoms followed by an acute onset of symptoms and signs of CS. Surgical resection and radiotherapy have led to 2.5 years of disease-free survival. Review of available medical literature suggests that there is generally good prognosis of ON associated with CS, with only two persons succumbing to the disease.

Portions of this case were presented at ENDO 2016, the Endocrine Society's 98th annual meeting and expo in Boston, Massachusetts, April 2016.⁹

Learning points

- ▶ Cushing's syndrome (CS) is a possible paraneoplastic manifestation of olfactory neuroblastoma.
- ▶ Rapid onset of CS is more characteristic of an ectopic adrenocorticotrophic hormone secretion presentation.
- ▶ Consider head and neck imaging in persons with nasal symptoms and acute onset CS.

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REFERENCES

- 1 Thompson LD. Olfactory neuroblastoma. *Head Neck Pathol* 2009;3:252–9.
- 2 Jethanamest D, Morris LG, Sikora AG, et al. Esthesioneuroblastoma: a population-based analysis of survival and prognostic factors. *Arch Otolaryngol Head Neck Surg* 2007;133:276–80.
- 3 Kunc M, Gabrych A, Czapiewski P, et al. Paraneoplastic syndromes in olfactory neuroblastoma. *Contemp Oncol* 2015;19:36–42.
- 4 Yu J, Koch CA, Patsalides A, et al. Ectopic Cushing's syndrome caused by an esthesioneuroblastoma. *Endocr Pract* 2004;10:119–24.
- 5 Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2008;93:1526–40.

- 6 Lopez JA, Kleinschmidt-Demasters Bk B, Sze CI, *et al.* Silent corticotroph adenomas: further clinical and pathological observations. *Hum Pathol* 2004;35:1137–47.
- 7 Koo BK, An JH, Jeon KH, *et al.* Two cases of ectopic adrenocorticotrophic hormone syndrome with olfactory neuroblastoma and literature review. *Endocr J* 2008;55:469–75.
- 8 Hyrcza MD, Ezzat S, Mete O, *et al.* Pituitary Adenomas Presenting as Sinonasal or Nasopharyngeal Masses: A Case Series Illustrating Potential Diagnostic Pitfalls. *Am J Surg Pathol* 2017;41:525–34.
- 9 Batacchi Z, Trikudanathan S. Adrenocorticotrophic Hormone-Producing Esthesioneuroblastoma. *Endocrine Reviews* 2016;37.(Suppl 2).

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