Recurrent Esthesioneuroblastoma Presenting as an ACTH Paraneoplastic Syndrome
S Rodgers, Y Moshel, I Mikolaenko, A Gilbert, R Babu

INTRODUCTION
Ectopic ACTH production causing Cushing Syndrome is a rare occurrence, such that only 10% of ACTH-dependent Cushing Syndrome results from ectopic ACTH production (1). Carcinoma of the lung represents the most frequent (up to 95%) cause of ectopic ACTH production. A source of ectopic ACTH production is not identified in 10% of cases. Esthesioneuroblastoma producing ACTH is an extremely rare occurrence with few reported cases in the literature (1). The first reported case of an ACTH producing Olfactory Neuroblastoma, leading to Cushing’s Syndrome was in 1994 by Arnesen, et al. (2). Olfactory Neuroblastoma also referred to as esthesioneuroblastoma represents 2-3% of nasal cancers (1,3). Only six cases of ACTH producing esthesioneuroblastoma have been reported in the literature (1,2,4,5,6,7).

CASE REPORT
INITIAL PRESENTATION AND HOSPITAL COURSE
A 51-year-old, right-handed, male presented initially with unremitting headache for several months. He also complained of anosmia and nasal congestion. Other than the anosmia he was neurologically intact on examination. A contrast enhanced brain MRI revealed a nasal mass that extended into anterior cranial base through the cribiform plate (Figure 1). The patient underwent a gross total resection of the lesion through a combined trans-cranial and trans-facial approach. The resection margins were clear of tumor on pathology and the post-operative MRI demonstrated complete resection of the contrast-enhancing tumor. Post-operatively, he underwent thirty-six cycles of radiation therapy.

TUMOR RECURRENCE- PRESENTATION AND HOSPITAL COURSE
5 years later, the patient presented to a local emergency department with right shoulder pain. Routine blood work revealed a serum potassium of 1.5 mEq/L and a serum bicarbonate of 40 mEq/L. He denied any symptoms of hypokalemia including lethargy or weakness. He denied any
headaches or other neurological symptoms and was intact on neurological exam. Further workup showed normal plasma aldosterone (8 ng/dL) and renin (0.9 ng/mL/hr) levels, and near normal afternoon cortisol levels (14.4 mcg/dL, normal range 1.7-14 mcg/dL) but MRI showed bilateral adrenal hyperplasia. These findings suggested that ACTH levels should be elevated, and testing revealed a markedly abnormal ACTH level of 948 pg/ml (ref range 7-69 pg/ml). CT scan of the chest did not reveal any findings suggestive of lung carcinoma.

MRI of the brain revealed an extradural contrast-enhancing lesion that extended from the anterior temporal convexity to the parietal convexity (Figure 1). An angiogram demonstrated an external carotid supply (Figure 1). The patient underwent craniotomy for resection of the new contrast enhancing extradural lesion. The tumor was resected along with a margin of attached dura and easily separated from the surface of the brain because of a preserved arachnoid plane. Post-operative MRI confirmed gross total resection of the contrast-enhancing lesion (Figure 1).

SECOND HISTOLOGICAL EXAMINATION

The second specimen was a pale tan firm mass measuring approximately 10.7 x 6.0 x 1.6 cm again well adherent to the dura (Figure 2). The tumor from the secondary resection had similar morphological and immunohistochemical features to the primary resection with lobular architecture and dense fibrous bands, consistent with esthesioneuroblastoma (Figure 2). The tumor cells demonstrated mild nuclear pleomorphism with few mitoses. The original primary and secondary resection specimens were stained with ACTH immunostain. The primary resection revealed focal positive staining for ACTH while the secondary specimen was diffusely and strongly positive for ACTH immunostain (Figure 2).
CLINICAL COURSE
Following resection of the tumor, repeat ACTH levels were obtained. By post-operative day 2, his ACTH level had fallen to 203 pg/mL, and by post-operative day 4, it dropped to 87 pg/mL. The patient was started on spironolactone 50mg three times a day, and his serum potassium rapidly corrected and his blood pressure returned to normal.

DISCUSSION
ACTH paraneoplastic syndrome develops when hypercortisolism develops from an extrasellar production of excessive ACTH by a tumor. Only 10% of hypercortisolism caused by ACTH overproduction is a result of ectopic ACTH secretion (1). The majority (95%) of ACTH paraneoplastic syndromes are caused by chest tumors such as carcinoid and oatcell. Others sources include gastrinoma, pheochromocytoma, and thymic. Even with CT/MRI, and occasionally an octreotide nuclear scan, the source of ectopic ACTH overproduction is sometimes not identified (1,8). In the present case, hypercortisolism was characterized by hypertension and hypokalemia. The presence of adrenal hyperplasia in the setting of normal aldosterone, normal renin and near-normal cortisol levels suggested a primary problem of ACTH overproduction and the extraordinary (20 fold) elevation of ACTH strongly suggested ectopic ACTH production rather than an anterior pituitary tumor. The past history of a brain tumor raised suspicion that a recurrent esthesioneuroblastoma was the source for the ectopic ACTH production.

Esthesioneuroblastoma have been reported in the literature (1-7). The treatment for such tumors primarily depends on gross total resection with adjuvant radiation therapy. The resolution of elevated hormone levels after gross total resection appears to alleviate symptoms and laboratory abnormalities of ACTH or anti-diuretic hormone overproduction.

Interestingly, serum levels of ACTH can be followed as a marker for tumor response to adjuvant therapy when gross total resection is not achieved. When gross total resection cannot be achieved, ACTH overproduction can be palliated with pharmacological inhibitors of corticosteroid production (e.g. metyrapone and ketoconazole) or with laproscopic bilateral adrenalectomy (1,5).

References
Author Information

Shaun D. Rodgers, MD
Department of Neurosurgery, New York University School of Medicine

Yaron A. Moshel, MD, PhD
Department of Neurosurgery, New York University School of Medicine

Irina Mikolaenko, MD
Department of Pathology, New York University School of Medicine

Alexander J. Gilbert
Department of Medicine, New York University School of Medicine

Ramesh P. Babu, MD
Department of Neurosurgery, New York University School of Medicine