Recurrent Esthesioneuroblastoma Presenting as an ACTH Paraneoplastic Syndrome

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Abstract

The authors report the case of a 51-year-old male that presented with hypertension and arm pain 5 years after combined transcranial and transfacial resection followed by radiotherapy for esthesioneuroblastoma. Laboratory studies revealed hypokalemia and elevated serum cortisol and ACTH levels. Brain magnetic resonance imaging (MRI) revealed a left-sided contrast-enhancing extra-axial dural-based lesion along the convexity. After resection of the convexity tumor, histological examination identified the lesion as recurrent esthesioneuroblastoma and serum ACTH and cortisol levels returned to near normal. Ectopic ACTH production from esthesioneuroblastoma is extremely rare and only six cases have been reported. This case report will describe the clinical presentation and pathology of recurrent esthesioneuroblastoma and review the literature.

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.

FIRST HISTOLOGICAL EXAMINATION

The specimen consisted of pale tan firm tissue attached to rubbery membranous dura. The tumor had invaded the dura, but did not unequivocally reach the intracranial margin. The tumor was composed of well-formed lobules of closely packed cells separated by a fibrous stroma. The tumor cells had uniformly round-to-oval nuclei with mild pleomorphism set in a finely fibrillar stroma. Nuclear chromatin varied from delicate to more coarse. Mitoses were inconspicuous. Rare Homer Wright rosettes were identified. The tumor demonstrated weak, but diffuse immunopositivity for synaptophysin and neurofilament protein. A minority of tumor cell nuclei were immunopositive for NEU-N (Figure 2). The pathology was consistent with esthesioneuroblastoma.

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).

Figure 1

Figure 1: A) Pre-operative MRI before the first resection demonstrating the contrast-enhancing nasal tumor extending to the anterior cranial base. B) Pre-operative MRI before the second resection demonstrating a convexity dural based contrast-enhancing mass. C) Pre-operative angiogram before the second resection demonstrating the middle meningeal supply to the tumor. D) Post-operative MRI after the second resection with no significant residual contrast-enhancing tumor.

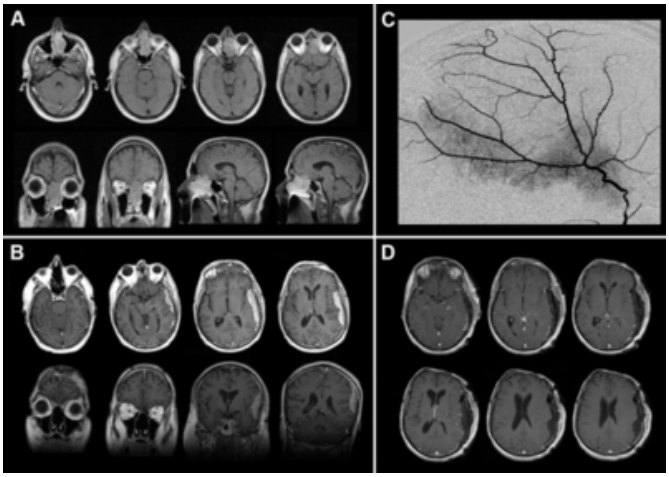
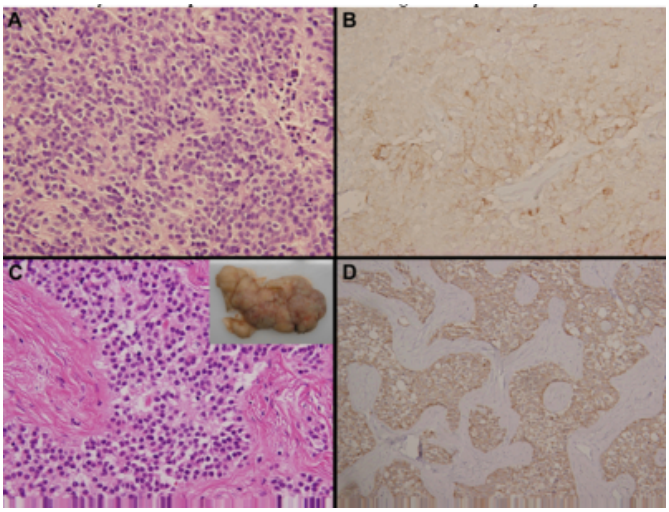


Figure 2

Figure 2: A) Hematoxylin and eosin stain of the primary resection specimen demonstrates features consistent with esthesioneuroblastoma composed of small round cells set in a fibrillar background and rare Homer-Wright rosettes. B) ACTH immunostain of the primary resection specimen shows focal weak immunopositivity . C) Hematoxylin and eosin stain of the secondary resection specimen reveals findings similar to the primary resection specimen, consistent with recurrent esthesioneuroblastoma. The inset is a photograph of the second resection gross specimen. D) ACTH immunostain of the secondary resection specimen shows diffuse strong immunopositivity.



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 is a rare nasal tumor and represents 2-3% of all endonasal tumors (1,3). The production of functional hormone from such tumors rarely occurs. Six cases of ACTH producing and 10 cases of SIADH producing 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).

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