Cushing's Syndrome: An Unusual Presentation of Olfactory Neuroblastoma

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ABSTRACT

A 48-year-old man presented with symptoms consistent with Cushing's syndrome. Subsequent laboratory studies revealed markedly elevated adrenocorticotrophic (ACTH) and cortisol levels, as well as a hypoklemic metabolic alkalosis. A pituitary MRI was performed, which revealed a normal pituitary; however, a large mass was seen centered in the ethmoid and paranasal sinuses with a significant amount of extension into surrounding structures. A biopsy was performed and pathology of the specimen was consistent with esthesioneuroblastoma. Immunohistochemical staining further defined the tumor as an ACTH-secreting esthesioneuroblastoma. After total resection of the mass and further treatment with adjuvant radiation therapy, the patient's symptoms completely resolved and the ACTH and cortisol levels were also greatly reduced. This case demonstrates the successful diagnosis and treatment of a rare neoplasm. Ectopic ACTH syndrome due to esthesioneuroblastoma is extremely uncommon with only five other cases being discussed in the literature.

KEYWORDS: Ectopic ACTH syndrome, Cushing's syndrome, olfactory neuroblastoma, esthesioneuroblastoma

Esthesioneuroblastoma is a rare malignant neoplasm of the nasal cavity thought to arise from olfactory neuroepithelium. Esthesioneuroblastomas were first described in 1924 by Berger et al and account for ~3% of intranasal tumors with an average 5-year survival rate of 45%.¹ Neuroepithelial tumors are characterized by small, round, blue cells. Vasoactive neuroepithelial tumors of the head and neck are rare, the most common of which are paragangliomas. Esthesioneuroblastoma has been

reported to cause Cushing's syndrome secondary to ectopic adrenocorticotrophic hormone (ACTH) secretion. Secretion-inappropriate antidiuretic hormone (SIADH) caused by esthesioneuroblastoma has also been reported.^{2,3}

Cushing's syndrome is a disorder of hypercortisolism which has a characteristic appearance (moon facies, buffalo hump, truncal obesity, and purple striae). Furthermore, it is associated with a variety of organ dysfunctions including

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cardiovascular, endocrine, neural, gastrointestinal, skin, and musculoskeletal. Ectopic secretion of ACTH accounts for ~10% of Cushing's syndrome etiologies. Ectopic ACTH syndrome due to esthesioneuroblastoma is extremely rare; there have been reports of five other cases in the literature.⁴⁻⁸ The following case is that of a 48-year-old Caucasian man presenting with Cushing's syndrome due to Kadish grade C, ACTH-secreting esthesioneuroblastoma.

CASE PRESENTATION

In late April 2006, a 48-year-old man presented to the emergency department with symptoms of leg edema, blurred vision, and general weakness of one week's duration. On physical exam, the patient was noted to have 2+ pitting edema on his lower extremities bilaterally and mildly elevated blood pressure (145/81 mm Hg). At the time of presentation, he did not appear severely cushingoid; however, he did notice progressive hyperpigmentation and facial rounding occurring over the past 2 years. Laboratory results revealed highly elevated ACTH and cortisol levels (ACTH = 648 pg/mL; AM cortisol = 137.9 µg/dL; 24-hour urine cortisol 11640.3 µg/24 hours total volume). In addition, the patient was also hypokalemic (2.1 mEq/L) and had a metabolic alkalosis (pH = 7.546, HCO₃ = 34 mEq/L). Dexamethasone suppression test was considered: however, in the presence of very high ACTH and cortisol levels, hypokalemia, and metabolic alkalosis, as well as clinical findings, a primary pituitary tumor or an ectopic ACTH syndrome was suspected, so the test was not performed.

Computed tomography (CT) scans of the chest, abdomen, and pelvis were normal except for two tiny lung nodules, hyperplastic adrenal glands, and osteopenia. A pituitary magnetic resonance image (MRI) showed a normal pituitary; however, there was a large, aggressive mass centered in the ethmoid paranasal sinuses (Fig. 1). The mass extended into the frontal sinus and maxillary sinuses, sparing the sphenoid sinus; it also bulged into the

Figure 1 Sagittal T1 image with gadolinium shows nasal cavity tumor attached to the cribriform plate.

anterior nasopharynx and extended through the cribriform plate and pushed against the inferior portion of the frontal lobe. Otolaryngology was consulted. A maxillofacial CT scan further characterized the soft-tissue mass having an intracranial portion of 1.8 × 1 cm and a paranasal sinus portion measuring 5 × 9 × 6 cm (Fig. 2). There was no involvement of the orbits. The MR/CT appearance

Figure 2 Coronal computed tomography scan with contrast shows bone destruction at the left cribriform plate with intracranial extension.

Figure 3 Synaptophysin stain. Positive brown esthesioneuroblastoma invades submucosal tissue, which lacks synaptophysin.

of the mass, in combination with the clinical and laboratory findings, was suspicious for esthesioneuroblastoma. A biopsy of the lesion and an octreotide scan were performed to confirm that the lesion was neuroendocrine in origin.

To control his metabolic abnormalities, the patient was treated with ketoconazole 400 mg twice daily preoperatively. He also required calcium, vitamin D, potassium, and phosphorus supplementation. Three weeks after his initial presentation, the patient underwent a combined bifrontal craniotomy and subcranial skull base approach to the anterior cranial fossa. Gross total resection was performed

Figure 4 Hematoxylin and eosin stain. Crowded, small fibrillar cells have round nuclei. Mitosis is in seen in the upper right portion of the figure.

Figure 5 Focally positive staining for adrenocorticotrophic hormone.

in a combined effort by the neurosurgery and otolaryngology services. The patient was treated with a stress dose of steroids postoperatively.

Grossly, the tumor was soft and multilobulated. Pathologic study and immunohistochemical staining of the resected tumor revealed a densely cellular neoplasm. Neoplastic cells were small, monotonously uniform, and had extended fibrillar cytoplasmic processes. Their nuclei were round with speckled chromatin and prominent nucleoli. Mitoses were evident. Neoplastic cells were abundantly positive for synaptophysin and S-100 protein (Figs. 3 and 4). The S-100 protein stain also highlighted very darkly stained sustentacular cells. There was focal expression of ACTH and chromogranin

Figure 6 Prominent adrenocorticotrophic hormone in perivascular regions.

A (Figs. 5 and 6). These findings represent an ACTH-secreting esthesioneuroblastoma.

The patient received adjuvant postoperative radiation treatments which included 60 Gy, and the periphery of the target received 54 Gy, all in 30 fractions, using intensity-modulated radiotherapy (IMRT). Following the operation, his ACTH level decreased to 26 pg/mL. He was discharged on postoperative day 4 on hydrocortisone 5 mg in the morning and 10 mg in the evening for secondary glucocorticoid deficiency because of prolonged ectopic ACTH secretion. When the patient finished the hydrocortisone course, he maintained a normal ACTH, morning plasma cortisol, and urine cortisol levels. Furthermore, his Cushing's syndrome symptoms completely resolved. A repeat MRI 6 months postoperatively demonstrated no evidence of recurrence.

DISCUSSION

Immunohistochemical staining was important in establishing the diagnosis of esthesioneuroblastoma. There is no specific immunohistochemical stain for esthesioneuroblastoma, but a typical staining profile can be useful. About 80% of these tumors are positive for neuron-specific enolase, chromogranin, and synaptophysin. S-100 protein will also stain positive. Esthesioneuroblastoma rarely stains positive for keratins. Esthesioneuroblastoma tumor cells stain negative for EMA (epithelial membrane antigen), tyrosinase, and myc-2 protein. These stains serve to identify esthesioneuroblastoma as well as eliminate other tumor types within the differential.⁹ In the case reviewed here, ACTH expression in the tumor was assessed in addition to synaptophysin, S-100 protein, chromogranin A, tyrosinase, myc-2, EMA, and cytokeratin. The tumor showed neoplastic cells abundantly positive for synaptophysin and S-100 protein. After establishing the diagnosis of esthesioneuroblastoma on the basis of structural and immunohistochemical features, ACTH stain-

ing was performed to determine if this tumor was also the source of the ectopic ACTH. The tumor expressed ACTH, particularly in perivascular neoplastic cells.

Cushing's syndrome is caused by (1) exogenous glucocorticoids, (2) hypothalamic-pituitary disorders, (3) primary adrenal disorders, and (4) ectopic secretion of ACTH. This is usually caused by small cell carcinomas of the lung, carcinoid tumors, pancreatic islet cell tumors, medullary thyroid carcinomas, and, rarely, paragangliomas. The diagnosis of ectopic ACTH syndrome secondary to esthesioneuroblastoma was established based on the presence of ACTH seen on immunohistochemical staining of the tumor, the disappearance of symptoms, as well as a decrease and normalization of plasma ACTH and cortisol levels after resection of the tumor.

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