ABSTRACT

Objective: To discuss the role of bilateral adrenalectomy in Cushing syndrome, as illustrated in a case of severe hypercortisolism that was unresponsive to combination agent medical therapy.

Methods: We report the clinical, laboratory, imaging, and pathologic findings in a patient with ectopic Cushing syndrome attributable to an adrenocorticotropic hormone (ACTH)-secreting neuroblastoma. In addition, we provide a literature review regarding olfactory neuroblastoma and discuss current and emerging therapeutic options for Cushing syndrome.

Results: A 59-year-old man presented with nasal congestion and neck swelling and was noted to have hypokalemia, hypertension, and hyperglycemia. Nasal biopsy demonstrated a poorly differentiated carcinoma with neuroendocrine features. He was subsequently diagnosed as having ACTH-dependent Cushing syndrome, but despite high-dose combination medical therapy, his condition rapidly deteriorated. Urgent bilateral adrenalectomy provided rapid control of the hypercortisolism, and the patient was later able to undergo an uncomplicated total macroscopic resection of his locally metastatic primary tumor.

Conclusion: This report describes the challenges in the diagnosis and management of ACTH-dependent Cushing syndrome and highlights the important role that bilateral adrenalectomy can still have in patients with severe hypercortisolism causing life-threatening complications. (Endocr Pract. 2012;18:e85-e90)

INTRODUCTION

Ectopic adrenocorticotropic hormone (ACTH)-secreting tumors account for 10% of cases of Cushing syndrome and are characterized by acute onset of hypercortisolism, signs of mineralocorticoid excess, weight loss, myopathy, and hyperpigmentation (1-8). Involved ectopic sites include the lungs, pancreas, thymus, and thyroid (1,2,4,7,8). We describe a case of ectopic Cushing syndrome attributable to an olfactory neuroblastoma that reminds us that even though bilateral adrenalectomy is not first-line therapy for most patients with Cushing syndrome, it may be a potentially lifesaving procedure in critically ill patients with hypercortisolism.

CASE PRESENTATION

A 59-year-old man presented with nasal congestion, tearing, periorbital edema, and neck swelling and was noted to have hypokalemia, hypertension, and hyperglycemia. Nasal examination and biopsy demonstrated a poorly differentiated carcinoma with neuroendocrine features. Carboplatin and etoposide chemotherapy induced an approximate 10% reduction in tumor size, but during a second cycle of treatment, he developed abdominal pain and chemotherapy was halted. Computed tomography demonstrated a perforated diverticulum and bilateral adrenal hyperplasia. Hemicolecetomy with colostomy.
placement was performed, and a work-up for Cushing syndrome was initiated. Substantially increased values for 24-hour urinary free cortisol (4,305 µg/d; reference range, <50), serum cortisol (60 µg/dL; reference range, 8 to 25), and plasma ACTH (565 pg/mL; reference range, 6 to 59) were found, and a diagnosis of ACTH-dependent Cushing syndrome was made. Ketoconazole (200 mg orally 3 times daily), insulin therapy, and potassium supplementation were initiated; however, hypokalemia and poor wound healing persisted, and he was transferred to our institution.

The patient was confined to a wheelchair and had cachexia, bilateral cervical lymphadenopathy, and purulent discharge from his pericoloectomy site. Positron emission tomography and computed tomography demonstrated enlarged fludeoxyglucose F 18-avid right submandibular glands, multiple enhancing neck lymph nodes, and paranasal sinus opacification (Fig. 1). Dynamic 3-T magnetic resonance imaging (MRI) of the pituitary showed no abnormalities. Despite use of an increased dosage of ketoconazole (400 mg 3 times daily) and addition of octreotide (200 mg 3 times daily), the biochemical features of hypercortisolism persisted (Table 1), and the patient’s clinical condition worsened. Metyrapone was not administered because it is not readily available in the United States. Therefore, urgent bilateral adrenalectomy was performed in an effort to salvage the patient. The patient’s hospital course was complicated by further intestinal microperforation, poor healing, and nephrogenic diabetes insipidus attributable to hypokalemia. Nonetheless, with resolution of the hypercortisolism and use of replacement glucocorticoid and mineralocorticoid therapy, the patient had a complete recovery.

Two months later, the patient underwent a craniotomy for definitive resection of the intradural and extradural skull base tumor and bilateral neck dissections. Pathology examination confirmed the presence of an esthesioneuroblastoma with nests and lobules of cells (Fig. 2 A) that had mild-to-moderately pleomorphic oval nuclei that were immunopositive for synaptophysin and chromogranin A (Fig. 2 B). An S-100 immunostain highlighted sustentacular cells at the periphery of the tumor lobules (Fig. 2 C). Moderate numbers of scattered cells showed generally

![Fig. 1. Radiographic imaging of the olfactory neuroblastoma. A. Contrast-enhanced magnetic resonance imaging (coronal view) of the brain, demonstrating a soft-tissue filling defect in the right nasal cavity (arrow). B. Fludeoxyglucose F 18 (FDG) positron emission tomography, exhibiting abnormal uptake in the right ethmoid cavity (arrow). C. Computed tomography of the neck, highlighting enhancing enlarged right cervical lymph nodes (arrow). D. Intense FDG activity is evident in the right cervical nodes, consistent with a metastatic poorly differentiated carcinoma (arrow).]
sparse immunoreactivity for ACTH (Fig. 2D). Cervical lymph nodes were extensively involved by tumor with similar histologic features. The proliferation marker Ki-67, which identifies cells in G1, G2/M, and S phase, was also examined and was estimated at 10%. The stained slides were digitally scanned with an Aperio ScanScope XT scanner (Aperio Technologies, Vista Park, California), and micrographs were captured at Aperio ImageScope ×20 and ×40 magnifications (approximately the equivalent of ×200 and ×400 magnification, respectively, of a microscope). Postoperatively, the plasma ACTH level declined from 232 to 5 pg/mL, consistent with ectopic ACTH secretion from the esthesioneuroblastoma (Table 1).

Nine months after bilateral adrenalectomy, the patient was walking with a cane, his hyperglycemia and hypertension had resolved, and the colostomy site had fully healed. The patient is free of macroscopic tumor and is currently undergoing adjuvant chemotherapy and radiotherapy.

**DISCUSSION**

This example of Cushing syndrome attributable to an olfactory neuroblastoma illustrates several diagnostic and treatment challenges. In particular, it highlights that although bilateral adrenalectomy is appropriately viewed as a last-resort treatment for hypercortisolism in most patients, in selected circumstances this strategy may be a potentially lifesaving therapy. Because of the patient’s nonspecific initial presentation, Cushing syndrome was not considered despite, in hindsight, signs of glucocorticoid excess. The absence of weight gain, central obesity, and striae contributed to the delay in diagnosis of Cushing syndrome in this patient, but these features are not always seen in rapidly progressive ectopic Cushing syndrome (2,4). Once Cushing syndrome was suspected, confirmation with elevated levels of urinary free cortisol and serum cortisol was not difficult, and a high plasma ACTH concentration suggested an ACTH-dependent cause (4,5).

The majority of cases of ACTH-dependent Cushing syndrome are due to a corticotroph pituitary tumor (that is, Cushing disease) (3-7,9,10). This patient, however, had no abnormalities on pituitary MRI, and in light of the tissue diagnosis of carcinoma with neuroendocrine features, ectopic production of ACTH was considered early. It must be remembered, however, that an MRI abnormality may not be demonstrable in up to 50% of cases of Cushing disease (4,5,7,11).

The primary objective in Cushing syndrome is to achieve a normal serum cortisol level and tumor control (2,6,8,9). This patient was essentially moribund with limited therapeutic options because impaired wound healing restricted further chemotherapy. Moreover, a definitive resection of the ACTH-secreting primary tumor was hindered by malnourishment and complications of hypercortisolism including wound dehiscence, hyperglycemia, recurrent infection, and metabolic abnormalities. In this rapidly deteriorating patient, quick normalization of cortisol levels was imperative to stabilize his condition and allow other definitive therapy (3,4). In some circumstances, medical therapy can rapidly control cortisol secretion, but steroidogenesis inhibitors such as ketoconazole, metyrapone, and mitotane are effective only for a short
period in up to 50% of patients. Because of its easier availability in the United States, we chose to use ketoconazole in our patient; nevertheless, even in combination with the somatostatin analogue octreotide, little improvement was seen (2-6,9,12).

In light of the patient’s grave medical condition, we elected to perform bilateral adrenalectomy for immediate control of the hypercortisolism. Historically, bilateral adrenalectomy performed by open laparotomy has been associated with a high morbidity of 40% and a mortality rate of 5.6% (13). Current minimally invasive laparoscopic bilateral adrenalectomy approaches, however, have decreased the morbidity and the perioperative complications to 15%, and the associated mortality is now similar to that for endoscopic endonasal pituitary surgical procedures at <1.5% (3,4,10,11,13). After bilateral adrenalectomy, patients require lifelong glucocorticoid and mineralocorticoid replacement that, although burdensome, is generally straightforward.

Olfactory neuroblastoma is rare, with an annual incidence of 0.4 to 1 in 1,000,000, and constitutes 3% to 10% of nasal malignant lesions (2,14-16). Most commonly, it manifests during the second and sixth decades of life with equal sex distribution and is associated with a 45% 5-year survival rate (2,14-17). Its cryptic location and nonspecific symptoms of congestion, epiphora, and epistaxis can delay diagnosis by at least 6 months (1,2,7,14-16). Because of the location close to the sella, esthesioneuroblastomas must be distinguished from pituitary adenomas that have extended downward into the nasal cavity or intracranial “ectopic” pituitary adenomas originating from rests of pharyngeal pituitary in the sphenoid sinus or clivus bone (1,2,8,14). Therefore, careful imaging and surgical biopsy with histopathologic review are often key for accurate diagnosis because, on microscopic examination, esthesioneuroblastomas exhibit strong immunopositivity for S-100, which distinguishes them from pituitary adenomas (16,17). Assessment of proliferation markers such as Ki-67 has been used to determine the grade in several neuroendocrine tumor subtypes, such as pancreatic neuroendocrine tumors, whereby low-grade tumors exhibit 1% to 2% and high-grade tumors demonstrate >20% of cells stained, with less well-defined intermediate-grade tumors between this range. Few studies, however, have assessed Ki-67 in esthesioneuroblastomas (14). Ectopic production of ACTH from these tumors is rare, although it imparts a more favorable prognosis because of earlier presentation of patients with hormonal manifestations (1,2,7,8,15).
Tumor recurrence is seen in 20% to 40% of patients and is usually local, although distant metastatic involvement by means of the lymphatic system to lung and bone occurs in 10% to 40% of patients (15,18). Recurrences, however, may not manifest for decades, and aggressive surgical resection and radiation therapy are warranted but may be limited in extensive metastatic disease (1,2,7,14,16). Other therapeutic options that have been tried include somatostatin analogues, chemotherapy, interferon-α, chemomobilization, and radio-frequency ablation, but these interventions have yielded varied results (2,16).

In the future, new medical agents may be available for treatment of Cushing syndrome and Cushing disease. Data from phase 2 clinical trials indicate that the glucocorticoid receptor antagonist mifepristone (RU-486) is effective in improving glycemic control and hypertension in patients with Cushing syndrome (3,5). Dose adjustment, however, may be challenging and made primarily on clinical grounds because, in light of the mode of action of the drug to block glucocorticoid receptors, signs of hypoadrenalism may be evident even in patients with elevated levels of serum cortisol (3,12). The novel somatostatin receptor ligand, pasireotide, exhibits high-affinity binding to the somatostatin receptor subtype 5, which is abundant in corticotroph pituitary tumors. This drug normalized urinary free cortisol in 17% of patients in a single-arm, 15-day, open-label clinical trial, although adverse effects including gastrointestinal discomfort and hyperglycemia were noted in 50% of patients (3,6,19,20). Other recent studies have used combination therapies and demonstrated that addition of cabergoline to pasireotide treatment improved urinary free cortisol normalization rates from 29% to 53%, and further addition of ketoconazole ultimately achieved urinary free cortisol normalization in 90% of the patients treated with any or all 3 of these agents (3,6,9). Stepwise use of multiple agents is common practice in hypertension and diabetes and may be a strategy worth consideration in treatment of hypercortisolism. Some of these agents, however, await approval by the US Food and Drug Administration, and further studies are needed to test the long-term efficacy of these regimens.

CONCLUSION

Overall, this case illustrates how severe hypercortisolism limited potentially curative therapy for an underlying ACTH-secreting esthesioneuroblastoma. Medical therapy did not offer satisfactory control of the hypercortisolism, but bilateral adrenalectomy provided rapid normalization of cortisol levels and ultimately allowed macroscopic surgical resection of the tumor and adjuvant therapy. Although bilateral adrenalectomy is appropriately not first-line therapy in most cases of ACTH-dependent Cushing syndrome, it can be the optimal choice when hypercortisolism is causing life-threatening complications. Modern laparoscopic approaches have dramatically improved the morbidity and mortality associated with bilateral adrenalectomy, and its rapidity in correcting the hypercortisolism was key to the ultimate success in recovery of our patient.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

REFERENCES


