**ABSTRACT**

Below is a carefully crafted and succinct introduction to the session recordings from the symposium, *Cushing’s Disease: When Surgery Fails*, which was presented on June 17, 2013 in San Francisco during the Endocrine Society’s 95th Annual Meeting & Exposition. This is a commentary which well summarizes the clinical questions and the talks designed to provide different clinical solutions.

**A CHALLENGING CLINICAL CASE**

A 25-year-old female presents with new onset hypertension, six months of proximal muscle weakness, facial hirsutism, irregular menses, and 30 pound weight gain over the prior year. Physical exam reveals increased truncal obesity, facial rounding, moderate supraclavicular adiposity and extremity wasting. Two 24-hour urine and 2 late night salivary cortisol levels were elevated 3-4 fold above the upper limit of normal, and 1 mg dexamethasone suppression test cortisol was 7.2 mcg/dl (normal less than 1.8 mcg/dl). Her ACTH level was 43 pg/ml. Pituitary MRI revealed a subtle 2 mm hypodensity; therefore, she underwent inferior petrosal sinus sampling to confirm localization, which indicated a pituitary source of autonomous ACTH. Transphenoidal pituitary resections were performed twice by a skilled pituitary surgeon and pathology confirmed resection of ACTH-positive pituitary adenoma; however, her urine cortisol levels remained elevated following surgery. Debate exists about the next steps in this patient’s management, with considerations including pituitary sella radiation therapy, medical management, or bilateral adrenalectomy. The choice of appropriate therapy for individuals with persistent hypercortisolemia following pituitary surgery depends on many factors, including age, gender, tumor size and location, future fertility goals, other medication use and comorbidities, and patient preference and resources.
Cushing’s Disease: WHEN SURGERY FAILS

INTRODUCTION
Cushing’s syndrome is an interesting and yet challenging disorder and because Cushing’s syndrome is a rare entity, most endocrinologists will see relatively few cases within their career; however, the diagnosis is considered in many individuals and a familiarity with specific presenting signs and symptoms is essential to guide appropriate screening for the disorder. A step-wise approach to establishing biochemical hypercortisolemia and localization of source is required, which dictates the choice of surgical intervention in most cases. When Cushing’s disease (pituitary-dependent Cushing’s syndrome) is diagnosed, transsphenoidal pituitary surgery by a skilled surgeon is the usual first step in management, as it frequently provides remission of hypercortisolemia with relatively few long-term negative effects. Unfortunately, surgery is not curative for all patients and recurrence after initial remission is not uncommon even many years following an apparently successful pituitary surgery [6]. Radiation therapy can be utilized in individuals with Cushing’s disease as it provides the potential for long-term remission. The choice of radiation modality, stereotactic radiosurgery versus fractionated radiation, the likelihood of producing remission, and the potential side effects of radiation must be considered. Although several medications to block adrenal steroidogenesis have historically been used in the treatment regimen of Cushing’s syndrome, recently two medications, pasireotide and mifepristone, have been approved for use in Cushing’s disease patients. As new medical therapies become available, understanding their role in the management of the Cushing’s patient and potential side effects is crucial.

BIOCHEMICAL DIAGNOSIS OF CUSHING’S DISEASE
The diagnosis of Cushing’s syndrome can be difficult in many patients because the usual presenting symptoms are common and nonspecific but actual Cushing’s syndrome is rare. This situation calls for a very thoughtful screening strategy to minimize false positive results, which includes identification of specific clinical signs and symptoms as an indication to proceed with biochemical testing. The recommended tests to establish hypercortisolemia include 24-hour urine cortisol, 1 mg overnight dexamethasone suppression testing or 2-day low dose dexamethasone suppression testing, and late night salivary cortisol sampling. Certain medical comorbidities and medications can confound these measures and borderline results require repeat testing to confirm hypercortisolemia. Subsequently, a non-suppressed ACTH level indicates ACTH-dependence. Further assessment with pituitary MRI imaging, high dose dexamethasone suppression testing, and possibly CRH stimulation testing may be used to distinguish between pituitary and ectopic ACTH production in some cases, but inferior petrosal sinus sampling is most accurate and may be used when pituitary-dependence is not certain [5].

SURGICAL MANAGEMENT OF CUSHING’S DISEASE
Transsphenoidal pituitary resection is the primary treatment modality for most individuals with Cushing’s disease. Successful resection of the corticotroph adenoma produces remission in many cases but long-term monitoring for recurrence is necessary. Post-operative transient adrenal insufficiency is common and requires glucocorticoid replacement until hypothalamic-pituitary-adrenal axis recovery occurs and assessment of other pituitary hormone axes after surgery is indicated. Bilateral adrenalectomy can be considered in cases of Cushing’s disease in which pituitary resection is not successful and other treatment options are either not effective or appropriate. Lifelong glucocorticoid and mineralocorticoid replacement is necessary and as well as monitoring for Nelson’s syndrome, symptomatic enlargement of the pituitary corticotroph adenoma [1].

RADIATION THERAPY IN THE TREATMENT OF CUSHING’S DISEASE
In individuals with large or rapidly growing corticotroph adenomas, radiation therapy is often a necessity. In the usual Cushing’s disease patient with a small residual tumor, radiation therapy, with photon or proton beam, can be considered and the mode of radiation, either fractionated or stereotactic radiosurgery, is dependent on the size and location of the tumor. Radiation therapy may provide a lasting remission of hypercortisolemia; however, radiation is not effective in all cases and in most cases there is a substantial delay between the time of radiation and the normalization of cortisol levels. Medical management of hypercortisolemia during this delay is usually required. Radiation frequently produces hypopituitarism over time and rare cases of neurologic and vascular injury and secondary tumors related to radiation have been reported [7].
MEDICAL MANAGEMENT OF CUSHING’S DISEASE

The medical management of Cushing’s disease can include several points of attack, including adrenal steroidogenesis inhibition (ketoconazole, metyrapone, mitotane, etomidate), suppression of ACTH (pasireotide, cabergoline), and glucocorticoid receptor antagonism (mifepristone). Combination medical approaches may also be utilized. While medical management has been routinely used as a bridge to a definitive therapy, such as bilateral adrenalectomy or while awaiting effectiveness of radiation, long-term medical management has not been extensively studied [3].

Each medical modality offers unique considerations with respect to monitoring, side effects, and drug-drug interactions. While long used as the primary medical therapy for hypercortisolemia, adrenal steroidogenesis inhibitors have variable efficacy and drug-specific side effects.

As a glucocorticoid receptor antagonist, mifepristone blocks the effects of hypercortisolemia but does not lower (and in some cases increases) serum cortisol levels. Monitoring of efficacy requires careful consideration of the effects of hypercortisolemia as the practitioner cannot rely on standard measures of blood, urine, or saliva cortisol levels to determine successful treatment. As such, this medication has been approved for use in individuals with hypercortisolemia and elevated blood glucose, as changes in blood glucose provide a biochemical means to monitor efficacy. Side effects of hypokalemia, hypertension, and uterine hyperplasia must be monitored [4].

Pasireotide is a somatostatin receptor agonist with efficacy in the treatment of Cushing’s disease due to suppression of autonomous ACTH and subsequently cortisol levels. The effectiveness of pasireotide is monitored with standard measures of urine, serum, and salivary cortisol levels. These medications may cause gastrointestinal symptoms and may suppress insulin release resulting in glucose intolerance or diabetes mellitus [2].

CONCLUSIONS

The main challenges of Cushing’s syndrome management include: initial consideration of the diagnosis, understanding the pitfalls of diagnostic testing, localizing the source of ACTH or cortisol excess, establishing an initial treatment approach, dealing with treatment failures or recurrence, and managing the effects of hypercortisolemia and the side effects of treatment. Initial treatment of Cushing’s disease usually entails pituitary surgery. When surgery proves unsuccessful, a very patient-specific treatment plan must be established which considers the short and long term effects of each subsequent treatment option including radiation therapy, medical management, and bilateral adrenalectomy. The advent of new medication options in the treatment armamentarium for Cushing’s disease is exciting for the endocrinologist but understanding the role and side effects of these medications is imperative for appropriate Cushing’s disease management.

REFERENCES


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