Recurrence of Cushing’s disease after bilateral adrenalectomy: A myth or reality?

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Abstract
Bilateral adrenalectomy usually results in lifelong primary adrenal insufficiency. Evidence exists that up to 34% of patients with Cushing’s disease (CD) have some degree of endogenous cortisol secretion after treatment; however, it is unusual that overt recurrence persists even after the removal of the replacement therapy. We present a case of a patient with an atypical corticotropinoma/carcinoma and CD recurrence after bilateral adrenalectomy. A 59-year-old man presented with CD in 2010 and underwent a transsphenoidal adenomectomy. Pathohistological evaluation suggested an 8 mm × 8 mm atypical corticotropinoma. CD recurred 8 months after surgery. A total hypophysectomy was performed, which led to complete remission, followed by recurrence 5 months later. Subsequently, a bilateral two-stage adrenalectomy was performed along with radiosurgical treatment. Postoperatively, the patient received glucocorticoid replacement therapy. 2 years after the adrenalectomy, the patient was diagnosed with Nelson’s syndrome. Fractionated radiotherapy was given, and ACTH levels slightly decreased, but urinary free cortisol (UFC) continued to increase. Glucocorticoid therapy was stopped, but UFC increased to 1400 nmol/24 h (normal range 54–319 nmol/24 h) 3 years after the adrenalectomy, accompanied by the recurrence of signs and symptoms of CD. Abdominal computed tomography showed a 4 cm large mass in the left adrenal bed suggestive of adrenal tissue, along with multiple liver lesions, without signs of another primary tumor. The patient died 5 years after initial diagnosis. This is the first case of recurrent CD after bilateral adrenalectomy. This report highlights the importance of long-term patient monitoring after total bilateral adrenalectomy and individual dosing of replacement therapy.

Key words: Recurrence; Cushing’s disease; pituitary carcinoma; bilateral adrenalectomy; nelson’s syndrome
1. Introduction

Bilateral adrenalectomy is used for patients with Cushing’s disease (CD) who underwent a non-curative surgery or as a life-preserving emergency treatment [1]. After the procedure, patients with persistently increased ACTH levels have been reported to regain detectable adrenal function [2-7]. We present a case of a patient with atypical corticotropinoma/carcinoma and the recurrence of CD accompanied by clinical signs and symptoms after total bilateral adrenalectomy.

2. Case Report

A 59-year-old man originally presented with CD in 2010. Increased level of cortisol (serum cortisol 08:00h 1518 nmol/L (normal range 171-536 nmol/L), 17:00 h 1659 nmol/L (normal range 64-327)) with a loss of circadian rhythm and increased level of ACTH (160.2 pmol/L, normal range 1.6-13.9 pmol/L) were found. Urinary free cortisol (UFC) was increased (2400 nmol/24 h, normal range 54-319 nmol/24 h). Magnetic resonance imaging (MRI) revealed intrasellar mass 8 mm × 8 mm suggestive of a microadenoma. Transsphenoidal selective adenomectomy was performed, and pathohistological evaluation was suggestive of atypical corticotropinoma (Ki-67 proliferation index of 7%, positive nuclear staining for p53). Despite some improvement in clinical signs, the patient had active CD (UFC 716 nmol/24 h). 8 months after the initial surgery, UFC rose to 8923 nmol/24 h and ACTH rose to 35.5 pmol/L (Figure 1).

MRI showed pituitary mass measuring 12 mm × 10 mm × 8 mm invading the left cavernous sinus. Total hypophysectomy led to complete remission, but recurrence occurred only 5 months later. We performed radiosurgical treatment of the remnant tumor mass, along with bilateral two-stage adrenalectomy. Pathohistological evaluation confirmed complete removal of the left adrenal gland but was inconclusive in the case of the right one. Postoperatively, the patient developed adrenal insufficiency, which required long-term glucocorticoid and mineralocorticoid replacement therapy (hydrocortisone 20 + 10 mg daily). 2 years after the adrenalectomy, the patient developed Nelson’s syndrome. He presented with diplopia, due to 15 mm × 9 mm pituitary tumor mass involving right cavernous sinus, accompanied with hyperpigmentation of the skin and increased ACTH level (125 pmol/L). Standard fractionated radiotherapy was performed, after which ACTH slightly decreased, but we observed continuous increase in UFC levels while taking hydrocortisone replacement. Replacement therapy was stopped, but UFC increased to 1400 nmol/24 h (serum cortisol level 08:00h 643 nmol/L, 17:00 h 336 nmol/L), accompanied by the recurrence of signs and symptoms of CD and complete vision loss. MRI showed dramatic progression of the pituitary tumor measuring 40 mm in the largest diameter, invading both optical nerves and extending to the frontal lobe (Figure 2a and b). Abdominal computed tomography showed 40 mm × 5 mm large mass in the left adrenal bed suggestive of adrenal tissue (Figure 2c), along with the multiple liver lesions (Figure 2d). Tumor markers were all within normal ranges, and besides corticotropinoma, there were no signs of another primary tumor. The patient died 5 years after the initial diagnosis and his family refused an autopsy.

3. Discussion

Total bilateral adrenalectomy is considered to be a definitive cure for CD [2], resulting in primary adrenal insufficiency requiring lifelong glucocorticoid and mineralocorticoid replacement therapy to prevent potentially fatal Addisonian crisis [3]. It is not mandatory to routinely measure UFC levels in patients taking hydrocortisone replacement therapy [3]. If necessary, UFC levels can be monitored approximately 7 days after initiation of hydrocortisone replacement (Figure 1).

Figure 1. Changes in patient’s ACTH and UFC after transsphenoidal selective adenomectomy (a), total hypophysectomy (b), bilateral two-stage adrenalectomy (c, d), and standard fractionated radiotherapy (e)
after the bilateral adrenalectomy, although long-term follow-up of electrolytes and metabolic parameters is recommended [4]. However, endogenous cortisol secretion has been described in up to 34% of the patients after bilateral adrenalectomy. All of these patients needed reduction of the hydrocortisone dose, but neither one patient showed clinical signs of CD [5,6]. To the best of our knowledge, this is the first case of a recurrent overt CD after bilateral adrenalectomy, which persisted even after the withdrawal of glucocorticoid replacement therapy. Cortisol producing tissue has been described as adrenal remnants after the procedure [5], or as an ectopic adrenal tissue [7]. Some authors suggest the possibility of ACTH driven hyperplasia of retained adrenal cortical cells [3] or hyperplasia of adrenal rest tissue in the testes [8]. In our case, an abdominal computerized tomography scan revealed a mass in the left adrenal bed suggestive of adrenal tissue. Pathohistological examination of the removed adrenal glands confirmed a complete removal of the left adrenal gland, which implies, in the absence of another ectopic adrenal tissue, that the detected adrenal bed tissue formed as a result of ACTH driven hyperplasia of retained cortical cells. This report highlights the importance of long-term surveillance for recurrent increased cortisol production in patients after total bilateral adrenalectomy, especially in patients with atypical corticotropinomas. It also advises against routine administration of full replacement doses and supports an individualized approach in determining the maintenance dose in patients with detected cortisol production.

**Author Contributions**

IV reviewed the previously published literature, wrote the article and gave the final approval. MČ and JMR participated in study design, acquisition of data, drafting the

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**Figure 2.** Coronal (a) and sagittal (b) T1-weighted contrast enhanced magnetic resonance images showing pituitary tumor measuring 40 mm in the largest diameter, invading both optical nerves and extending to the frontal lobe. Abdominal computed tomography is showing 40 mm × 5 mm large mass in the left adrenal bed suggestive of adrenal tissue (c), along with the liver metastasis (d).
article, and gave the final approval. IK gave an idea for the case study, participated in drafting the article and gave the final approval. HIP performed radiological evaluation and gave the final approval. VC performed the surgery and was engaged in patient’s follow-up, and gave the final approval. LP performed pathohistological analyses and gave the final approval. MV and GM were engaged in endocrinological evaluations and follow-up and gave the final approval.

References


