The role of bilateral adrenalectomy in the treatment of refractory Cushing’s disease

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Cushing’s syndrome (CS) results from sustained exposure to excessive levels of free glucocorticoids. One of the main causes of CS is excessive adrenocorticotropic hormone (ACTH) secretion by tumors in the pituitary gland (Cushing’s disease [CD]). Cushing’s disease and its associated hypercortisolism have a breadth of debilitating symptoms associated with an increased mortality rate, warranting urgent treatment. Currently, the first line of treatment for CD is transsphenoidal surgery (TSS), with excellent long-term results. Transsphenoidal resections performed by experienced surgeons have shown remission rates ranging from 70% to 90%. However, some patients do not achieve normalization of their hypercortisolemic state after TSS and continue to have persistent or recurrent CD. For these patients, various therapeutical options after failed TSS include repeat TSS, radiotherapy, medical therapy, and bilateral adrenalectomy (BLA). Bilateral adrenalectomy has been shown to be a safe and effective treatment modality for persistent or recurrent CD with an immediate and definitive cure of the hypercortisolemic state. BLA was traditionally performed through an open approach, but since the advent of laparoscopic adrenalectomy, the laparoscopic approach has become the surgical method of choice. Advances in technology, refinement in surgical skills, competency in adrenopathology, and emphasis on multidisciplinary collaborations have greatly reduced morbidity and mortality associated with adrenalectomy surgery in a high-risk patient population. In this article, the authors review the role of BLA in the treatment of refractory CD. The clinical indications, current surgical and endocrinological results reported in the literature, surgical technique (open vs laparoscopic), drawbacks, and complications of BLA are discussed.

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Key words: bilateral adrenalectomy; refractory Cushing’s disease; laparoscopic adrenalectomy; failed transsphenoidal surgery; Nelson’s syndrome

Cushing’s syndrome (CS) results from the chronic exposure to excessive concentrations of glucocorticoids. More than 80% of cases are adrenocorticotropic hormone (ACTH) dependent, and the majority of these are due to excessive ACTH production from a pituitary adenoma, referred to as Cushing’s disease (CD). The remaining 20% or so are ACTH independent and are caused by excessive cortisol secretion by adrenal tumors or by nonpituitary neuroendocrine tumors (ectopic ACTH secretion), which also increases cortisol production.

Cushing’s syndrome has a myriad of debilitating effects on one’s physiology and well-being. These effects include cortisol-induced complications, such as increased cardiovascular risks and thromboembolism, musculoskeletal impairments, immunosuppression, and diabetes. It is associated with increased morbidity and mortality, psychological effects, and ultimately decreased quality of life. Patients may present with characteristic features of CS, including moon facies, central obesity, wide purple striae, proximal muscle weakness, and the development of a posterior cervical fat pad, or “buffalo hump.” Those patients with untreated CS have a 5-fold increased mortality rate with a mean survival time from initial presentation of 5 years, and therefore effective treatment is critical. Predominant causes of death are due to cardiovascular complications and infections. Cushing’s syndrome also

ABBREVIATIONS ACTH = adrenocorticotropic hormone; BLA = bilateral adrenalectomy; CD = Cushing’s disease; CRH = corticotropin-releasing hormone; CS = Cushing’s syndrome; SRS = stereotactic radiosurgery; TSS = transsphenoidal surgery.

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takes an incredible toll on a patient's emotional well-being, leading to psychiatric complications and suicide.6 The objectives in the treatment of CS are to: 1) reverse the clinical consequences of hypercortisolism; 2) normalize biochemistry and prevent inappropriate ACTH and cortisol secretion; 3) prevent recurrence; and 4) minimize treatment morbidity.4,43

During the 1950s, bilateral adrenalectomy (BLA) was the choice of therapy for CD, boasting a high success rate in reversing hypercortisolism, ranging from 88% to 100%.21 Eventually it was found that there was significant risk of developing Nelson’s syndrome after BLA, where risks started outweighing the benefits and thus its role as first-line treatment was abandoned.4 Soon after, with the advent of transsphenoidal surgery (TSS) and recognition of the pituitary gland as the primary source of the problem, the treatment strategy shifted to a more targeted therapy toward the aberrant pituitary source. Currently, the first-line treatment of CD is transsphenoidal resection of the pituitary adenoma.16,20,22,24,27

Transsphenoidal surgery for the treatment of CD has served as an effective treatment option, with remission rates ranging from 70% to 90% when performed by experienced surgeons.9,13,24,32,33,35,36,38–41 However, persistent and recurrent disease does occur in 11.5% to 25% of patients.3,21,24,43,50 Because of the debilitating manifestations and the increased morbidity and mortality of persistent CD, it is critical that physicians are aware of alternative treatment options after failed TSS. These options include repeat TSS, radiation therapy including Gamma Knife radiosurgery, medical therapy, and BLA.24 Although BLA is no longer the first-line treatment for CD, it continues to play a valuable role in the treatment of CD, especially in the management of more challenging patients who are refractory to TSS or other therapeutic options.44

Indications for BLA

BLA may be indicated as a surgical therapeutic option after failed attempts at treating refractory CD, including repeat TSS, radiation therapy or stereotactic radiosurgery (SRS), and medical therapy.1,2,4,5 This may occur when there is persistent hypercortisolism and residual tumor after primary transsphenoidal resection, or if the tumor recurs after initial biochemical remission. Nevertheless, adrenalectomy is typically reserved as a treatment modality only after therapy directed at the pituitary gland has failed,19 such as repeat TSS or radiosurgery if applicable. In ACTH-dependent CS, the adrenal gland is not the source of the problem but instead stands as the affected end organ. However, adrenalectomy can play a role as initial therapy for those patients with severe hypercortisolism, life-threatening disease, unresectable pituitary tumors, or when a tumor is metastatic or locally invasive.1

Occasionally, BLA represents the preferred option for younger female patients who are concerned with their fertility, where their only other therapeutic option is complete hypophysectomy.25 BLA is also used to alleviate the effects of ectopic ACTH secretion when the source of ACTH secretion cannot be localized or excised, or when the side effects of adrenolytic medications are intolerable.10,17,27

Role of BLA in Refractory Cushing’s Disease

While TSS is the first-line treatment for CD, it is not always successful due to various factors. One of the factors may be a large pituitary lesion that invades crucial structures such as the cavernous sinus, hindering proper complete resection. ACTH-secreting microadenomas may be so small that they escape identification and resection during surgery.52 The major advantage of BLA is that it provides immediate and effective control of the hypercortisolism state. It has been documented to be a safe and definitive treatment for patients with refractory CD who have unsuccessfully attempted multiple treatment options or require immediate reversal of hypercortisolism.24

As previously mentioned, other treatment alternatives are available after failed TSS for CD. Repeat TSS is a therapeutic option for persistent CS but comes with an increased risk of inducing panhypopituitarism as well as the implications of a second surgery.52 Although TSS of ACTH-secreting adenomas has shown high initial remission rates of 64%–93%, long-term remission rates are lower and range between 44% and 79%.7,15,50–52 Repeat transsphenoidal approaches also present with more complications due to scar tissue formation and potential loss of anatomical references.50 Radiation therapy, including conventional radiotherapy as well as SRS and fractionated stereotactic radiotherapy, is another secondary treatment option. Unfortunately, results present very slowly, taking up to 2 years,23 with high failure rates. Radiation therapy also carries the risk of causing posterior pituitary insufficiency, including hypothyroidism, hypogonadism, or growth hormone deficiency.55 A study by Wilson et al. showed that only 1 of 36 patients achieved biochemical remission after SRS and 9 demonstrated biochemical improvement but did not achieve serum targets.51 Medical therapy is rarely used as initial therapy. It is typically used as adjuvant therapy in recurrent or persistent CD or acts as an alternative bridging treatment until radiation therapy takes effect.24,25 Ketonazole, a steroid synthesis inhibitor, is commonly used and shows normalization or reduction in urinary free cortisol in 43% to 83% of patients.25 Other drugs such as ACTH-release modulators (i.e., bromocriptine) or glucocorticoid receptor antagonists are available but have short-lived efficacy.23 In general, medical therapy is poorly tolerated due to the adverse side effects of chronic therapy.15 Additionally, medical therapy is only palliative and does not serve as a definitive curative treatment because discontinuation of medical treatment will result in the recurrence of symptoms.4,22 A study by Morris et al. demonstrated that patients who were treated only medically with steroids were more likely to die of Cushing’s-related sequelae, whereas those who additionally underwent adrenalectomy (steroidogenesis inhibition + BLA) were not.27

Bilateral adrenalectomy therefore plays a crucial role in the treatment of refractory CD and provides prompt and reliable relief of hypercortisolism. However, BLA mandates lifelong glucocorticoid and mineralocorticoid replacement. Individuals who undergo unilateral adrenalectomies for aldosteronoma, pheochromocytoma, or large nonfunctioning tumors do not routinely require glucocorticoid and mineralocorticoid replacement therapy.
On the other hand, patients proceeding with adrenalectomies as treatment for refractory CD undergo bilateral adrenalectomy in which lifelong hormonal management is necessary. Proper administration of exogenous glucocorticoids is required to maintain hormonal functioning and balance. Because in CD the pituitary gland is the origin of disease, routine observation of growth and secretary function of the pituitary gland using MRI and ACTH measurements remains essential.

Open Versus Laparoscopic Approach

Since the introduction of the first laparoscopic adrenalectomy in 1992, the adrenalectomy procedure has been revolutionized, transitioning from predominantly an open to a laparoscopic approach. There are many benefits of the laparoscopic approach, including reduced length of recovery and hospitalization time, lower postoperative morbidity and decreased analgesic requirement postoperatively, and greater patient satisfaction. An analysis of 3100 patients in Elfenbein et al.’s percentage of neuromuscular complaints and chronic back pain.20 Because in CD the pituitary gland is the origin of disease, routine observation of growth and secretary function of the pituitary gland using MRI and ACTH measurements remains essential.

However, a disadvantage to this approach is the need to reposition the patient for a bilateral procedure. On the other hand, the anterior transabdominal approach allows for a bilateral adrenalectomy to be performed without repositioning the patient and also yields a conventional view of the abdominal cavity. A disadvantage of this approach is that it requires insertion of additional ports and has been reported to increase operative time.

A more direct access to the adrenal glands is provided by the retroperitoneal approach. In addition, no repositioning of the patient is required for a bilateral adrenalectomy, which may reduce operative time, and any abdominal adhesions from previous abdominal surgeries can be avoided. Consequently, exploration of the abdominal cavity is unavailable for concomitant pathology. Because working space is more limited in this approach, dissection and exposure are more difficult and therefore may not be appropriate for larger lesions. This approach may also be more difficult, especially in patients with CD as they have more retroperitoneal fat.

Lal and Duh compared the lateral transabdominal and posterior approaches in a series of 36 nonrandomized patients and found no difference in the mean operative time, morbidity, or hospital length of stay between the two groups of patients. It was noted, though, that the posterior approach was more difficult to teach and required routine intraoperative ultrasonography.

Because patients with CS are predisposed to poor wound healing, laparoscopic adrenal surgery presents an ideal surgical approach because it avoids large incisions and is minimally invasive. The magnification during laparoscopic adrenalectomy also allows for better visibility of the surgical field, leading to a decreased risk of leaving behind adrenal remnants. With CS, most adrenal lesions are small and pathologically benign, and so are well suited for laparoscopic excision. In addition, patients with CS typically present with increased adipose tissue, and for this reason the laparoscopic approach may be more appealing than an open laparotomy.

Laparoscopic adrenalectomy is contraindicated when adrenal carcinoma is suspected, as there is a concern of intraoperative tumor spillage and incomplete tumor clearance. It is also not recommended for large tumors because the risk of malignancy increases with size, and larger tumors are more arduous to remove.

Sometimes due to a patient’s physical characteristic or scarring from prior surgeries, laparoscopic adrenalectomy may not be recommended. Obesity can interfere with the proper identification of anatomy and may lead to difficulty in dissection during laparoscopic surgery. According to the NIH, obesity is defined as body mass index measurements greater than or equal to 30 kg/m². A study by Chow et al. showed that all patients requiring conversion to an open approach were obese. Similarly, of 22 patients who underwent laparoscopic adrenalectomy, 1 patient was converted to an open surgery because of morbid obesity in a study by Acosta and colleagues.

It is important to note that laparoscopic adrenalectomy is not easier or quicker and general anesthesia is still required. This procedure requires considerable time and effort, and expert surgeons and interdisciplinary collabo-
rations for an effective surgery. However, in the long term, laparoscopic adrenalectomy provides greater benefits to the patient and society (as discussed above) compared with the open approach.48

Laparoscopic adrenalectomy has been accepted as the standard of treatment for a majority of adrenal pathologies, especially with benign masses less than 6 cm in size and less than 100 g in weight. Masses up to 12–15 cm that are well encapsulated, without local invasion or nodular involvement, have also been operated on with great success.34 The laparoscopic approach is recommended for patients requiring bilateral adrenalectomy for the management of ACTH-dependent CS with persistent hypercortisolism.8,26

Published Studies of BLA for Cushing’s Disease

Bilateral adrenalectomy has been shown to be a safe and effective treatment for refractory CD.1,18,26,31,44,46 Several studies have demonstrated successful clinical outcomes after BLA, including improvement of Cushing’s-specific comorbidities such as hypertension, diabetes mellitus, osteoporosis, and muscle weakness.8,31,44 The published results of contemporary surgical series of BLA for CD from 2002 to 2014 are summarized in Table 1. Overall, the remission rate was 100% with a morbidity rate ranging from 6% to 26% and a follow-up duration ranging from 29 to 132 months. The rate of developing Nelson’s syndrome after BLA for CD ranged from 0% to 33%. In a recent systematic analysis of 24 published studies (768 patients) from 1981 to 2012, the average incidence of developing Nelson’s syndrome after BLA for CS was 21% (range 0%–47%).37

In a study by Oßwald et al., all 50 patients who underwent BLA for CD were found to be in remission, and all Cushing’s-specific comorbidities, except for psychiatric diseases, improved significantly.31 A recent series of 21 patients who underwent laparoscopic adrenalectomy for CS also demonstrated normalization of hormones in all patients, with no deaths or major postoperative complications and a morbidity rate of 6.3%.10 Smith et al. also demonstrated excellent survival and clinical results with BLA in patients with CD. In their series of 40 patients who underwent BLA for persistent CD after failed TSS, all the patients achieved clinical reversal of hypercortisolism, including patients with ectopic adrenal tissue. There were no operative or 30-day deaths, one 90-day death, and morbidities were observed in 18% of the patients. Such morbidities may include instances of prolonged ventilation, urinary tract infections, wound infections, incisional hernias, or arrhythmia. Their study demonstrated an all-cause survival rate of 97% at 1 year, and 87% at 5 years.44 Ding et al. also demonstrated survival rates of nearly 90% at 5 years, in which the main cause of death was due to cardiovascular anomalies well outside of the perioperative time period.11

With advancements in surgical technology, refinements in surgical technique, and improvements in perioperative management, anesthetic management, and understanding of adrenal pathophysiology, morbidity and mortality rates associated with adrenal surgery in patients with CS and CD have dramatically reduced.1,48

Quality of Life

Without treatment, CD or CS takes an incredible toll on the patient’s physical and mental well-being. Although patients experience a clinical reversal of hypercortisolism and an improvement in their health status after BLA, they continue to have a poorer health status than the general population. In a study by Hawn et al., 81% of patients reported in a survey that their health was improved after BLA, but they scored substantially lower on the 36-Item Short-Form Health Survey compared with the general population. A feeling of poorer health status is not limited to those after treatment of CD with BLA, but has also been noted in other treatment options as well.19 Overall, patients believe that their health status is better compared with 1 year before BLA. Quality of life questionnaires completed by 28 BLA patients in a study by Smith et al. also demonstrated similar results, in which 86% of the patients experienced an improvement in their health and 68% reported that their health posed no hindrance to moderate activities. The most common complaint observed among patients was fatigue.44

Pitfalls of BLA

General Risks

Individuals with CD and CS represent a special population of patients because their metabolic dysfunction leaves them vulnerable to decreased wound healing, increased risk of postoperative infections caused by a compromised immune system, deep venous thrombosis, and pulmonary embolism. Consequently, a higher rate of surgical morbidity and mortality is expected.1 Complication/morbidity rates and types of complications noted in recent published surgical series of BLA for CD are summarized in Table 2. In addition, CD patients usually are obese or hold excess fatty tissue that may make surgery and complete gland resection more difficult.1 As discussed above, because of these factors, the laparoscopic approach for BLA is well suited for patients with CD as it allows minimal tissue trauma and greater magnification of the surgical field.8

Residual adrenocortical function has also been known to occur even after intended total adrenalectomy. This may occur due to adrenal remnants left during surgery or the presence of accessory adrenal tissue. If the patient harbors an ectopic ACTH-secreting lesion and it is not excised, the patient will also experience persistent CD despite complete adrenal gland removal.44 Therefore it is important to pay careful attention and achieve optimal visualization to allow for complete resection of the adrenal gland and periadrenal fat.

Patients with CD are in a poorer health status and have a higher risk of encountering complications, but the revolution of sophisticated technology and surgical skills, and a better understanding of adrenal pathology, have allowed laparoscopic adrenalectomy to be a successful option in the treatment of CD. Despite these setbacks, many studies have confirmed BLA as a safe and effective treatment for
CD refractory to TSS with a low rate of morbidity and mortality and good long-term survival.\textsuperscript{27,31,44,49}

**Nelson’s Syndrome**

Development of Nelson’s syndrome after BLA is a consistent postoperative concern.\textsuperscript{21,24,44} In 1958 Nelson and colleagues first reported a patient with resolution of CS symptoms after BLA. Three years later, the patient developed hyperpigmentation and a pituitary tumor, and Nelson concluded that the “development of a pituitary tumor is a possible sequela of bilateral adrenalectomy for Cushing’s syndrome.”\textsuperscript{19} Nelson’s syndrome is characterized by elevated serum ACTH levels, hyperpigmentation, progressively enlarging pituitary tumors that tend to be invasive and rather aggressive in their growth pattern, and in rare cases, may develop into pituitary carcinomas.\textsuperscript{24,44} It is believed that the corticotroph adenoma cells that were primarily responsible for CD serve to be the source of the tumor that eventually grows and leads to Nelson’s syndrome development. Another school of thought questions if the pituitary ACTH adenoma tumor progression reflects a more aggressive molecular programming of the corticotrophic tumors.\textsuperscript{5}

With the complete removal of adrenal tissue, there is a loss of negative feedback control of serum cortisol on the hypothalamus and pituitary gland, leading to the development of Nelson’s syndrome (Fig. 1).\textsuperscript{5,44} Cortisol levels that previously suppressed hypothalamic corticotropin-releasing hormone (CRH) normalize after BLA, resulting in an increase in CRH production. Because the definition of Nelson’s syndrome used in the literature is not consistent, there are often difficulties comparing rates of Nelson’s syndrome development across patient series, and rates may vary.\textsuperscript{44} The risk of developing Nelson’s syndrome after BLA, depending on the follow-up length, has been re-

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<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients Undergoing BLA</th>
<th>No. of Patients Undergoing BLA for CD*</th>
<th>Morbidity (%)\textsuperscript{†}</th>
<th>30-Day Mortality (%)</th>
<th>Nelson’s Syndrome (%)</th>
<th>Mean FU (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chow et al., 2008</td>
<td>59</td>
<td>42</td>
<td>17</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ding et al., 2010</td>
<td>43</td>
<td>43</td>
<td>15</td>
<td>0</td>
<td>18</td>
<td>48.5</td>
</tr>
<tr>
<td>Gil-Cárdenas et al., 2007</td>
<td>39</td>
<td>39</td>
<td>NA</td>
<td>0</td>
<td>28</td>
<td>53</td>
</tr>
<tr>
<td>Hawn et al., 2002</td>
<td>18</td>
<td>18</td>
<td>16</td>
<td>0</td>
<td>5</td>
<td>29</td>
</tr>
<tr>
<td>Ößwald et al., 2014</td>
<td>50</td>
<td>34</td>
<td>6</td>
<td>4</td>
<td>24</td>
<td>132</td>
</tr>
<tr>
<td>Pugliese et al., 2008</td>
<td>11</td>
<td>8</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Smith et al., 2009</td>
<td>40</td>
<td>40</td>
<td>18</td>
<td>0</td>
<td>33</td>
<td>60</td>
</tr>
<tr>
<td>Takata et al., 2008</td>
<td>30</td>
<td>16</td>
<td>13</td>
<td>0</td>
<td>NA</td>
<td>31</td>
</tr>
<tr>
<td>Tiyadatah et al., 2012</td>
<td>19</td>
<td>19</td>
<td>26</td>
<td>5</td>
<td>17</td>
<td>32.6</td>
</tr>
</tbody>
</table>

FU = follow-up; NA = not available
\* Results in this chart are for patients undergoing BLA specifically for CD. Patients undergoing BLA for other diseases, such as pheochromocytoma and primary adrenal tumors, were omitted from the table.
\textsuperscript{†} Remission was achieved in 100% in all studies; remission was generally defined as biochemical resolution and/or absence of clinical evidence of persistent or recurrent disease or hypercortisolism after BLA.

**TABLE 2. Summary of morbidity/complications of published contemporary series evaluating outcomes of BLA for CD**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients Undergoing BLA for CD</th>
<th>Morbidity (%)</th>
<th>Morbidity/Complication Type (no. of cases)\textsuperscript{*}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chow et al., 2008</td>
<td>42</td>
<td>17</td>
<td>Wound infection, wound hematoma, pneumonia, prolonged ventilation, myocardial infarction, hydropneumothorax, thromboembolism\textsuperscript{†}</td>
</tr>
<tr>
<td>Ding et al., 2010</td>
<td>43</td>
<td>15</td>
<td>Urinary tract infection, wound infection, pneumonia\textsuperscript{†}</td>
</tr>
<tr>
<td>Gil-Cárdenas et al., 2007</td>
<td>39</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hawn et al., 2002</td>
<td>18</td>
<td>16</td>
<td>Intraoperative complication of colotomy (1), pancreatic pseudocyst (1), hemorrhage (1)</td>
</tr>
<tr>
<td>Ößwald et al., 2014</td>
<td>34</td>
<td>6</td>
<td>Infections (2), thromboembolism (1)</td>
</tr>
<tr>
<td>Pugliese et al., 2008</td>
<td>8</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Smith et al., 2009</td>
<td>40</td>
<td>18</td>
<td>Incisional hernias (3), wound infections (2), hemotherax (1), urinary tract infection (1), prolonged ventilator wean (1), arrhythmia (1), stroke (1), operative hemorrhage (1)</td>
</tr>
<tr>
<td>Takata et al., 2008</td>
<td>16</td>
<td>13</td>
<td>Pneumonia (1), infection (1)</td>
</tr>
<tr>
<td>Tiyadatah et al., 2012</td>
<td>19</td>
<td>26</td>
<td>Wound infection (2), port site hernia (1), pleural effusion (1), atelectasis (1)</td>
</tr>
</tbody>
</table>

\textsuperscript{*} Complications are postoperative unless otherwise noted.
\textsuperscript{†} Number of cases of complications not specified.
FIG. 1. Diagram of the hypothalamic-pituitary-adrenal axis. BLA eliminates the ability of adrenal glands to secrete cortisol. It also removes the negative feedback provided by cortisol on ACTH secretion by the anterior pituitary gland and CRH secretion by the hypothalamus. Proper hormonal replacement therapy will be required.

References


Conclusions

Bilateral adrenalectomy is a safe and effective therapeutic option for refractory CD. Laparoscopic surgery is currently recognized as the standard approach for BLA in most patients with CD, with the lateral transperitoneal technique as the most common laparoscopic approach to the adrenal gland. Because of the loss of negative feedback, the risk of development of Nelson’s syndrome remains an omnipresent event. Lifelong glucocorticoid and mineralocorticoid replacement therapy and long-term routine endocrinological care is required after BLA. After weighing the risks and benefits, BLA stands as a valuable treatment choice as it provides immediate and definitive control of the hypercortisolemic state.

Author Contributions
Conception and design: Liu, Wong. Acquisition of data: Wong. Analysis and interpretation of data: Wong. Drafting the article: Wong. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Liu. Administrative/technical/material support: Liu, Eloy. Study supervision: Liu, Eloy.

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