Role of Adrenalectomy in Ectopic ACTH Syndrome

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Abstract. Evaluation of adrenalectomy in patients diagnosed with ectopic ACTH syndrome was studied. Twenty-three clinical cases diagnosed with ectopic ACTH syndrome were analyzed at Chinese Academy of Medical Sciences and Peking Union Medical College Hospital (PUMCH). Cases consisted of 14 males and 9 females, with mean age of 38 years. All 23 cases had positive clinical, biochemical and radiology evidence for diagnosis of Cushing’s syndrome. Sixteen of the 23 cases were treated with total adrenalectomy and the remaining 7 were treated without surgical intervention. Sixteen cases, having no identifiable source of ectopic hormone production, experienced resolution of presenting signs and symptoms after undergoing bilateral or unilateral total adrenalectomy; 1-year survival was 67%, 2-year survival 41% and 5-year survival 15%. In patients treated conservatively without surgical intervention, 1-year survival was 0%. In patients with no identifiable source of ectopic hormone production, bilateral adrenalectomy followed by hormone replacement treatment is effective.

Key words: ACTH syndrome, Ectopic, Adrenal gland

ECTOPIC ACTH syndrome (EA) applies to an endogenous hypercortisolism condition sustained by a non-pituitary ACTH-secreting tumor. It poses major diagnostic challenges by imitating clinical manifestations of pituitary-dependent Cushing’s syndrome (CS), producing severe, life-threatening hypercortisolism. EA is associated with a variety of solid tumors, mostly of neuroendocrine origin, accounting for approximately 15% of all cases of endogenous CS [1]. In patients with pulmonary small cell carcinoma, prognosis is poor regardless of therapeutic modality. By contrast, in non-small cell cases of EA, tumors are much less aggressive, and hypercortisolism control becomes a paramount therapeutic issue. Whenever possible, these tumors should be removed surgically. However, in some patients the tumor is occult or metastatic, and resection is not possible. Treatments targeting the adrenal glands are necessary when ACTH source cannot be removed or treated.

Patients and Methods

We reviewed medical records of hypercortisolism patients diagnosed and treated for CS at Peking Union Medical College Hospital (PUMCH) between 1990 and 2002. Amongst the 289 patients with Cushing’s syndrome that were admitted to our hospital, 37 were EA. Of the 37 EA patients, 14 patients were treated with resection of ACTH-secreting tumors, 16 underwent adrenalectomy and 7 were treated with aminoglutethimide. Here, we analysed the 16 patients treated with adrenalectomy, comparing therapeutic effect with the 7 patients treated with aminoglutethimide.

All 23 patients (14 male and 9 female, mean age 38 years, range 14–65 years) were interviewed and examined for clinical signs and symptoms of CS.
Nineteen (83%) patients experienced hypertension requiring antihypertensive treatment. A total of 18 patients (21%) required either insulin or oral hypoglycemic agents for diabetes mellitus. Of 9 menstruating women, 6 (67%) complained of amenorrhea. All 23 patients had high levels of 24 hour urinary-free cortisol, and 19 (83%) patients failed suppression using a high dosage of dexamethasone. Plasma ACTH levels were 75–1033 pg/ml, mean 236 pg/ml.

Chest X-rays, abdominal and chest computed tomography (CT) or magnetic resonance imaging (MRI), pituitary MRI examinations were carried out in all cases. All cases had normal pituitary MRI scanning results. From chest CTs, we observed 4 cases of ectopic ACTH tumor, 3 in the lungs and 1 in the thymus gland. These 4 patients experienced clinical deterioration and hence did not undergo ectopic ACTH tumor resection. One patient had a normal chest CT scan, but from transfemoral catheterization of the femoral vein gradation sampling ACTH, we found the plasma ACTH levels in the azygous vein were much higher than in the internal jugular vein, with ratio 2.8 (normal ratio<1.5). We considered an ectopic ACTH tumor in the thoracic gland suggesting resection but patient declined surgical treatment. Another patient underwent interfemur biopsy of mass, the results of which indicated neuroendocrine tumor, but the patient refused further surgery of all sorts. A third patient underwent cervical lymph node biopsy, and again the results indicated a neuroendocrine tumor; however, the patient was a negative candidate for surgery due to extremely poor clinical conditions. All 7 patients undergoing conservative treatment were treated with aminoglutethimide, given dosages of 0.25 g bid to 0.5 g tid.

Only 1 case from the 16 patients selected for surgery had positive findings identifying ectopic tumor in the lungs from a chest CT. Of the 16 surgical candidates, 13 patients underwent bilateral total adrenalectomy, and 3 patients underwent unilateral total adrenalectomy. One patient was considered EA from inferior petrosal sinus sampling (IPSS), but localization of tumor was unclear; the patient underwent bilateral total adrenalectomy, the pathology report of which indicated bilateral adrenal cortical nodule hyperplasia. Another patient underwent pituitary gland exploration with no obvious findings. The patient then underwent right total adrenalectomy with amelioration of symptoms but CS recurred after one year; the patient later underwent resection of left adrenal gland, with satisfactory surgical results, and the pathological report indicated bilateral adrenal cortical nodule hyperplasia. A third patient, who underwent bilateral total adrenalectomy, had a pathology report indicating left adrenal cortical nodule hyperplasia and diffuse hyperplasia of right adrenal cortex. The remaining 13 patients, including 10 patients who underwent bilateral total adrenalectomy and 3 patients with right total adrenalectomy, were all adrenal cortical diffuse hyperplasia. CS symptoms and manifestations were all relieved. One patient was later discovered to have a mass present in the right lung followed by right upper lobe resection. Pathology indicated carcinoid of bronchus, and his plasma ACTH levels decreased following surgery but was still higher than normal standards. Eight months later, CS symptoms recurred, hence we considered another ectopic tumor was present or tumor recurrence had occurred, but we could not locate the tumor through radiology imaging. Thus an exploratory right adrenalectomy was performed and CS symptoms were relieved. For all patients treated with bilateral total adrenalectomy, we chose to perform a 2-stage procedure, first right adrenalectomy through lumbar incision followed by left adrenalectomy 2 weeks later. No patient died during the perioperative period. All patients were treated with hormone replacement regimens.

Clinical features of the 7 patients treated with aminogluthethimide and the 16 patients treated with adrenalectomy are indicated in Table 1.

Calculation of cumulative survival was obtained using the Kaplan-Meier method. Comparisons of the survival curves between groups were accomplished by log-rank test.

**Results**

Patients were followed up until December 2002 by outpatient clinic visits, correspondence or phone interviews. Of the 7 patients treated with aminogluthethimide, an adrenolytic drug, one patient was lost in follow-up after discharge (most likely deceased), and the remaining 6 patients’ drug administration period was 2 months to 4 months. Only 3 patients had serum and urinary cortisol results data 1 week or 1 month after treatment. Levels of serum and urinary cortisol after treatment were lower than before treatment: after 1 week, serum cortisol of two patients decreased 13%–15%, and urinary cortisol decreased 17%–45%, but
still not within normal range; after 1 month, serum cortisol of one patient decreased 63%, urinary cortisol decreased 47% (For serum/urinary cortisol data of the aminoglutethimide group please refer to Table 2). All patients died within 2–4 months after discharge; 3 patients died due to pulmonary infection, 1 of cerebrovascular incident and 2 due to cardiovascular incident; 1-year survival was 0%.

Sixteen patients treated with bilateral total adrenalectomy had better outcomes. The 1-, 2-, and 5-year survival rates were 67%, 41%, and 15%, respectively, were significantly better than the aminoglutethimide treatment group, P<0.001 (Fig. 1). Twelve patients endured until the latest follow-up (mean 2.9 years; range 0.2–7.4 years). Of the three patients treated with right total adrenalectomy, 24-hour urinary free cortisol (UFC) levels decreased, but were still higher than normal level. One patient was diagnosed with bronchial carcinoid later undergoing right upper lobe resection. Eight months later, the patient’s CS symptoms recurred, and this was followed by adrenalectomy of his right adrenal gland and CS symptoms were relieved; he survived 1.9 years post surgery, but 24-hour UFC level increased. We suggested adrenalectomy of the left adrenal gland but patient refused further surgical treat-

Table 1. Clinical features of 16 adrenalectomy patients and 7 aminoglutethimide patients

<table>
<thead>
<tr>
<th></th>
<th>Serum kalium (mmol/l)</th>
<th>Serum cortisol (ug/dl)</th>
<th>24 hour urinary free cortisol (ug/24 hour)</th>
<th>Serum ACTH (pg/ml)</th>
<th>High dosage of dexamethasone suppression test</th>
<th>Radiology Imaging: Tumor Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenalectomy group</td>
<td>3.2 ± 1.4</td>
<td>45 ± 17</td>
<td>457 ± 305</td>
<td>216 ± 182</td>
<td>86% suppressed</td>
<td>Chest CTs: lungs 3, thymus gland 1. Transfemoral catheterization of the femoral vein gradation sampling ACTH: thoracic gland 1. Two cases: negative chest CT, biopsy indicated neuroendocrine tumor.</td>
</tr>
<tr>
<td>Aminoglutethimide group</td>
<td>3.4 ± 1.3</td>
<td>42 ± 21</td>
<td>512 ± 274</td>
<td>247 ± 136</td>
<td>81% suppressed</td>
<td>Chest CT: lung 1</td>
</tr>
</tbody>
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Table 2. Serum/Urinary Cortisol Data of Aminoglutethimide Group

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>1 week after Treatment</th>
<th>Before treatment</th>
<th>1 week after Treatment</th>
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<tr>
<td>Serum cortisol (ug/dl)</td>
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<td>1</td>
<td>40</td>
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<td>6</td>
<td>57</td>
<td>/</td>
<td>213</td>
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</table>

* One month after treatment.

Fig. 1. Cumulative survival (Kaplan-Meier) of 16 patients undergoing adrenalectomy and 7 patients treated with aminoglutethimide.
ment. One patient personally elected for 2-stage adrenalectomy first performing right total adrenalectomy 0.2 years prior and then left adrenal gland resection later. We lost follow up contact of one right adrenalectomy patient. Of the 13 patients treated with bilateral total adrenalectomy, 1 patient was lost during follow-up, the remaining 12 patients were monitored and followed a strict steroid (prednisone) replacement treatment regimens with improved quality of life compared to their preoperative standards. Three patients died between 1.2 and 3.9 years (mean 2.4 years); all patients presented extensive metastases and death due to cardiovascular causes. Of the 12 patients requiring antihypertensive medication before surgery, 9 (75%) had complete resolution of symptoms and either required no antihypertensive treatment or reduced medications after surgery. Eight (80%) of 10 diabetic patients requiring either insulin or oral hypoglycemic medications either needed no medications or switched from subdermal insulin injections to oral hypoglycemic agents post operation. Three (75%) of the 4 patients complaining of amenorrhea resumed normal menstrual cycles.

Discussion

CS caused by ectopic ACTH production poses major challenges diagnostically due to its mimick-manifestations compared to the pituitary-dependent form of CS, producing severe, life-threatening hypercortisolemia. The link between cancer and CS was first reported in 1928 [2]. It was not until the 1960s that a connection was made between ACTH-dependent CS and certain non-pituitary tumors. It was recognized that neoplasms may acquire the ability to secrete substances not normally secreted from the tissue in which they originate [3]. Ectopic ACTH production resulting in CS is associated with a variety of solid tumors, mostly of neuroendocrinologic origin [4]. Indeed, Odell et al. [5] postulated all tumors endocrine or not, make proopiomelanocortin, an ACTH precursor, and other protein markers. Thus, hormonal endocrine syndromes are not manifestations of “ectopic hormone production”, but represent cancer-induced amplification of a property that is normally present in the cells from which the cancer originated. There are roughly two types of EA, one associated with overt malignancies and the other with occult neoplasms. The prototype of the first condition is CS sustained by small-cell lung carcinoma (SCLC), while bronchial carcinoid tumors are the most common occult sources of ACTH. It occurs in approximately 15% of all patients with this syndrome [6]. Causes of EA include SCLC, carcinoid tumors (lungs, thymus, gastrointestinal tract), islet cell tumors, pheochromocytoma and a long list of miscellaneous tumors (paraganglioma, prostate, breast, kidney, stomach and melanoma). SCLC in combination with EA has poor prognosis, with positive diagnosis established through standard chest radiography. Other ACTH-producing tumors of neuroendocrinologic origin are more difficult to diagnose [7].

Differential diagnosis is challenging because both carcinoids and pituitary microadenomas are difficult to detect even with sophisticated imaging procedures. Bronchial carcinoids are the ectopic ACTH-producing tumor most likely to elude detection over prolonged periods because of its small size and its unusual location in the middle third of the lung, adjacent to pulmonary vasculature from which it cannot be differentiated [8]. The gold standard for differential diagnosis is the contemporary sampling from a peripheral vein and both the inferior petrosal sinuses, direct pituitary effluents, for ACTH measurements. In the event of pituitary Cushing, a center to periphery gradient in ACTH concentrations is found, while in the ectopic Cushing there is no gradient [9]. One patient who underwent surgery using IPSS, had results supporting the diagnosis of EA. This is technically demanding and a very expensive procedure that should be performed only by experienced neuroradiologists to avoid misplacement of the catheters or unilateral cannulation of the petrosal sinuses, direct pituitary effluents, for ACTH measurements. Compared to this, Reimondo et al. suggested corticotrophin-releasing hormone tests were the most reliable noninvasive method to differentiate the pituitary from EA secretions in CS [12].

Location of ectopic ACTH-secreting tumors can be extremely difficult and continues to be a challenge for endocrinologists. The optimal treatment of EA involves resection or complete destruction of the ACTH-secreting neoplasm, a goal that cannot always be achieved. Aniszewski et al. found that only 12% of the patients had a resectable tumor that could be localized at the time CS was diagnosed [7]. In non-small cell cases of EA, the tumors are much less aggressive, and control of the hypercortisolism becomes the paramount therapeutic issue. According to a study published in
1952 by Plotz et al., up to 50% of patients with CS died within 5 years of presentation. The cause of death was primarily overwhelming infection in 46.6% of the cases; cardiovascular events were a close second at 40% [13]. But the most recent evaluation of patients treated with bilateral adrenalectomy for CS reported an overall 5-year survival rate of 66%–70% [14]. And so bilateral adrenalectomy is effective in treating CS. Though patient survival with EA was significantly worse than that of the CS group, the role of adrenalectomy is obvious in patients with EA. From our results, for the seven patients managed without surgical intervention, survival did not exceed 1 year. As for the 16 cases treated with bilateral or unilateral total adrenalectomy, resolution of presenting signs and symptoms were obvious, and survival rates fell into the various categories: 1-year survival was 67%, 2-year survival 41% and 5-year survival 15%. We considered the differences in prognosis between bilateral adrenalectomy and aminoglutethimide therapy to be reflected partly by selection bias (general conditions prior to treatment), as well as small sample size and heterogeneity. Moreover, those reasons might also explain that the efficiency of aminoglutethimide in our study was lower compared to previous study. In our hospital, only aminoglutethimide and ketoconazole are available. Compared to aminoglutethimide, ketoconazole has greater hepatotoxicity, hence we only selected use of aminoglutethimide taking into consideration the possibility of insufficiency, thus posing a possible explanation for unsatisfactory results for the seven patients not treated with adrenalectomy.

Aniszewski et al. found that the mean survival for the patients without surgical intervention after the diagnosis of CS was 0.6 year, much less than that of the patients treated with adrenalectomy (4.9 years) [7]. O’Riordain et al. found that in patients with ectopic ACTH production, the 1-, 2-, and 5-year survival rate was 67%, 44%, and 39%, respectively [15]. It was slightly better than our results. Bilateral adrenalectomy offers prompt biochemical treatment of hypercortisolism [16]. It is useful not only in occult tumors, but also in patients with recurrent tumor that could not be resected. Patients’ quality of lives were on a par with the general population, and health improvements were obvious in most cases [16]. Resolution of signs and symptoms of hypercortisolism were successful in our study.

All patients who underwent surgery experienced the posterior approach. Within these two years, laparoscopic bilateral adrenalectomy for Cushing’s disease was performed in our hospital, and we believed laparoscopy could represent an ideal approach.

In the three patients treated with unilateral adrenalectomy, the clinical signs and hypercortisolism symptoms were partly alleviated, but consequently required bilateral adrenalectomy. Subtotal adrenalectomy was first suggested by Priestley et al. in 1951 [17]. Successful adrenal transplantation has been performed as far back as 1951 with the use of embryonic adrenal tissue [18]. Recently autotransplantation has been attempted by many groups, and in spite of mixed reports bilateral adrenalectomy with adrenal autotransplantation remains a potential therapeutic option. Theoretically, effective autotransplantation provides an endogenous source of corticosteroids, eliminating the need for replacement therapy, rendering Addisonian crisis rare. It is encouraging to learn of successful functioning autografts [19]. We chose to first resect the right adrenal gland, since we think the left adrenal central vein is better than the right side; this is very important in autotransplantation. We hope that one day we will be able to perform left subtotal adrenalectomy and autotransplantation. Much has yet to be done to elucidate the factors which would optimize graft functions, to determine the response of functioning grafts, and to assess the long-term outcome for patients undergoing autotransplantation.

In conclusion, to most patients with no identifiable source of ectopic hormone production, bilateral adrenalectomy with hormonal replacement is effective. Operation should not be delayed, as operative risks increase with severity of hypercortisolism.

References


