Usefulness and Limitations of Unilateral Adrenalectomy for ACTH-independent Macronodular Adrenal Hyperplasia in a Patient with Poor Glycemic Control

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Abstract

Adrenocorticotropic hormone (ACTH)-independent macronodular adrenal hyperplasia (AIMAH) is a rare disease which causes Cushing’s syndrome. Bilateral adrenalectomy has been recommended as the treatment of choice for AIMAH. However, bilaterally adrenalectomized patients require lifelong steroid replacement therapy. Therefore, an increasing number of patients have undergone unilateral adrenalectomy for AIMAH. We report a case of AIMAH due to refractory diabetes in whom unilateral adrenalectomy initially yielded good diabetes control, but in whom poor glycemic control developed after 5 years, requiring eventual additional contralateral adrenalectomy. In elderly patients with AIMAH, one-stage bilateral adrenalectomy may be the treatment of choice.

Key words: ACTH-independent macronodular adrenal hyperplasia, Cushing’s syndrome

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Introduction

Adrenocorticotropic hormone (ACTH)-independent macronodular adrenal hyperplasia (AIMAH) is a relatively rare disease which causes Cushing’s syndrome (1). Bilateral adrenalectomy is considered the treatment of choice (1) and it is usually effective. However, it necessitates lifelong corticosteroid replacement therapy, which if discontinued, can result in life-threatening adrenal insufficiency.

It has recently been reported that good glycemic control was achieved in AIMAH patients who underwent unilateral adrenalectomy (2-4). The advantage of unilateral adrenalectomy is that 1 adrenal gland remains, making it possible to avoid lifelong hormone replacement. Therefore, it has been proposed as a new treatment for AIMAH (2-4).

We report a case of Cushing’s syndrome due to refractory diabetes in whom unilateral adrenalectomy initially yielded good diabetes control, but in whom poor glycemic control developed after 5 years, requiring eventual additional contralateral adrenalectomy.

Case Report

A 75-year-old woman was found to have diabetes in 1994 (at age 65) and was followed up thereafter at a local hospital. Initially, her glycated hemoglobin (HbA1c) level was in the range of 6% to 7%, according to the criteria of the National Glycohemoglobin Standardization Program (NGSP), but her glycemic control deteriorated from 1999 onward and her HbA1c level rose to 12% in 2002. Therefore, insulin therapy was initiated for worsening diabetes. Facial and lower leg edema then developed and she was admitted to our department in 2004 with suspected Cushing’s syndrome.

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Her ACTH level was below the detectable limit, and there was no evidence of a circadian rhythm of serum cortisol. A dexamethasone suppression test did not show any evidence of cortisol suppression with either 1 mg or 8 mg dexamethasone, and an abdominal computed tomographic (CT) scan revealed bunched enlargement of both adrenal glands (Fig. 1). We therefore diagnosed Cushing’s syndrome with suspected AIMAH on the basis of the CT findings. We performed various loading tests, but food intake did not significantly affect her cortisol level. A furosemide loading test followed by walking showed a 151% increase in her cortisol level (positive response), while an angiotensin receptor blocker loading test showed a 28% increase in her cortisol level (partial response).

After being given a diagnosis of AIMAH, the patient underwent resection of the left adrenal gland (which was larger than the right adrenal gland on CT images) (Fig. 1) in 2004. The histopathological findings of the resected specimen were consistent with AIMAH. Postoperatively, her basal secretion of cortisol returned to a normal level (8.2 μg/dL) (Fig. 2). She did not receive hydrocortisone replacement postoperatively. At that time, right adrenalectomy was considered, but written informed consent could not be obtained from the patient or her family regarding the need for postoperative lifelong cortisol replacement therapy. Therefore, she continued to receive insulin therapy and was followed up.

During the subsequent 4 years, she required a regular small dose of insulin to achieve good glycemic control, with an HbA1c level (NGSP criteria) of approximately 5.8%. However, her diabetes rapidly worsened in the summer of 2009, and her HbA1c level (NGSP criteria) rose to 9.1% in November of the same year. Her cortisol level rapidly increased in parallel (Fig. 2). Cushing’s syndrome was suspected owing to increased cortisol production from her remaining right adrenal gland. We initiated oral trilostane in December 2009, but an increase in dosage did not improve her HbA1c level (9.2%). Therefore, she was admitted to our Diabetes Division for further evaluation and treatment.

On admission, her height was 151.2 cm and her weight was 48.3 kg, with a body mass index of 21.2. Her consciousness was clear, her blood pressure was 127/88 mm Hg, and her pulse was 84 beats/min and regular. Her temperature was 35.5°C and her respiratory rate was 18 breaths/min. Her tongue was not dry and her thyroid gland was not palpable. On admission, her heart sounds were clear, without audible murmurs, her breath sounds were also clear and no rales were audible. Her abdomen was flat and soft, and neither the liver nor the spleen was palpable. There was no evidence of pretibial edema and her bilateral patellar and Achilles tendon reflexes were normal. She did not have a moon face, buffalo hump, or skin striae, but showed obesity.
in her trunk and thin extremities (Table 1).

Further CT and magnetic resonance imaging revealed enlargement of the remaining right adrenal gland (Fig. 1). Her plasma ACTH level was below the detectable limit, and her subsequent diabetes exacerbation. Therefore, metyrapone was ineffective. However, metyrapone was effective for the preoperative control of hypercortisolism.

As the present patient was elderly (75 years old) and initially did not give written informed consent regarding the need for cortisol replacement therapy after adrenalectomy, she therefore underwent unilateral adrenalectomy. As a result, good glycemic control was maintained for 4 years, although she was not completely weaned from insulin. However, subsequently, her diabetes gradually worsened and increasing doses of insulin did not improve her glycemic control. We concluded that her worsening diabetes was due to the exacerbation of Cushing’s syndrome. CT at that time revealed enlargement of the remaining right adrenal gland, suggesting a close association of the increase in the volume of this remaining adrenal gland with an increase in cortisol secretion and her subsequent diabetes exacerbation.

To treat the exacerbation of Cushing’s syndrome, the patient was given triostane orally, but an increasing dose was

AIMAH was first described in 1964 by Kirschner et al (5). Cushing’s syndrome which causes secondary diabetes is usually due to adrenal adenoma, although AIMAH is rare with an incidence of 1% in Cushing’s syndrome cases (1). Most patients with AIMAH exhibit typical features of Cushing’s syndrome, such as those observed in the present case, however a patient in whom AIMAH was diagnosed on the basis of diabetes, hypertension, and a manic episode has also been reported (6). Bilateral adrenalectomy has been recommended as the treatment of choice for AIMAH (1, 7). However, bilaterally adrenalectomized patients require lifelong steroid replacement therapy. If the replacement therapy is discontinued, life-threatening adrenal insufficiency can develop quickly.

The number of elderly patients who have undergone bilateral adrenalectomy for AIMAH has increased in recent years, and there is concern that compliance with oral corticosteroid treatment has decreased. Therefore, an increasing number of patients have undergone unilateral adrenalectomy for AIMAH and have then been followed up. It has been reported that patients who have undergone unilateral adrenalectomy can achieve favorable long-term glycemic control. Kageyama et al. reported good control of cortisol for 4 years in a patient who underwent right total adrenalectomy and left subtotal (2/3) adrenalectomy (8).

As the present patient was elderly (75 years old) and initially did not give written informed consent regarding the need for cortisol replacement therapy after adrenalectomy, she therefore underwent unilateral adrenalectomy. As a result, good glycemic control was maintained for 4 years, although she was not completely weaned from insulin. However, subsequently, her diabetes gradually worsened and increasing doses of insulin did not improve her glycemic control. We concluded that her worsening diabetes was due to the exacerbation of Cushing’s syndrome. CT at that time revealed enlargement of the remaining right adrenal gland, suggesting a close association of the increase in the volume of this remaining adrenal gland with an increase in cortisol secretion and her subsequent diabetes exacerbation.

To treat the exacerbation of Cushing’s syndrome, the patient was given triostane orally, but an increasing dose was
In the current case, metyrapone was administered to control the patient’s hypercortisolism, which led to a reduction in the dose of insulin required and confirmed the effect of cortisol synthesis inhibition by metyrapone.

Eventually, as written informed consent was obtained from both the patient and her family, bilateral adrenalectomy was performed. The patient was not completely weaned from insulin and requires the continued administration of an ultra-rapid-acting type of insulin, but she has maintained good glycemic control with an HbA1c level (NGSP criteria) of 7% to 8%. Therefore, it is unlikely that her diabetes was due to Cushing’s syndrome alone. However, the fact that glycemic control deteriorated after a 5-year period of good glycemic control following unilateral adrenalectomy suggests that enlargement of the remaining adrenal gland resulted in a further increase in cortisol hypersecretion, leading to the exacerbation of secondary diabetes.

As previously described, the conventional treatment for AIMAH has been bilateral adrenalectomy, which necessitates lifelong hormone replacement therapy. However, it has recently been reported that some patients with AIMAH undergo unilateral adrenalectomy and are then followed up (2-4). This treatment has the great advantage of not requiring hormone replacement therapy (3). It was further reported that in cases in which the left and right adrenal glands differed in size, unilateral adrenalectomy of the larger adrenal gland was more effective (12).

However, in the current case, plasma glucose control rapidly worsened 5 years after surgery. This suggests that unilateral adrenalectomy in elderly patients with AIMAH may result in the postponement of additional resection of the remaining adrenal gland, and such postponement is associated with a progressive decrease in systemic functional reserves in elderly patients, who may have increased risks associated with undergoing surgery and receiving anesthesia. In the present case, stenosis in 2 coronary arteries was identified preoperatively, thereby increasing the risk of surgery. Moreover, 1 year after the 2nd operation, the patient was hospitalized for treatment of a moderate cerebral infarction. Judging from these results, the operation described in the current report may have been the last opportunity in which surgery was feasible. Therefore, when selecting surgical procedures for AIMAH, age at onset and the level of cortisol secretion should be considered. Unilateral adrenalectomy may be indicated in young patients, but one-stage bilateral adrenalectomy may be preferable for elderly patients.

Oral metyrapone administration in place of surgery is also effective for the treatment of AIMAH (11). Recently, metyrapone was approved as a curative agent for Cushing’s syndrome in Japan. However, although metyrapone has a potent steroid synthesis-inhibiting effect, patients are at a high risk of developing adrenal insufficiency as an adverse effect because the dose is difficult to adjust. Mitotane is also effective for Cushing’s syndrome (13). However, mitotane is intended for the primary treatment of adrenal gland cancer, and has common adverse effects of nausea and vomiting.

Table 1. Clinical Data on Admission

<table>
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<tr>
<th>Parameter</th>
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Figure 3. A. The resected adrenal gland was yellowish and consisted of multiple nodules of various sizes. B. Hematoxylin and Eosin staining of the resected right adrenal gland showed the growth of large cortical cells with clear cytoplasm and insular patterns of compact, small, cytoplasm-poor cells.

Ineffective. Trilostane is one of the few steroid synthesis inhibitors approved for use in Japan. However, its therapeutic effect has been reported to be variable (9), and it was ineffective in the current case. To the best of our knowledge, there has only been 1 report on the long-term efficacy of trilostane for AIMAH (10).

On the other hand, metyrapone, which was previously used as a diagnostic agent to evaluate the ACTH-secreting function of the pituitary gland, has often been used for the preoperative control of hypercortisolism because its steroid synthesis-inhibiting effect is stronger than that of trilostane. Omori et al. also reported that metyrapone was effective in the treatment of Cushing’s syndrome due to AIMAH (11).
addition, the price of mitotane is very high in Japan, namely, 6 times that of metyrapone and 170 times that of hydrocortisone, when considered as an alternative postoperatively. Therefore, the use of mitotane is limited, and we must carefully consider whether metyrapone and mitotane, as therapeutic agents for Cushing’s syndrome, may be useful only as a secondary treatment to avoid surgery.

Kageyama et al. reported an AIMAH patient who was undergoing treatment for skin cancer and who received subtotal resection of the adrenal glands, preserving one-third of the left adrenal gland. The patient has been doing well for 4 years, with normal cortisol levels at the time of reporting (8). In the present case, the partial resection of the right adrenal gland as a second operation of choice was also taken into consideration.

However, it is not easy to determine the resection extent preoperatively. If the resected area is insufficient, another operation may be necessary. This is clearly not desirable in elderly patients such as in the present case, or if the patient has arteriosclerotic diseases such as cardiovascular complications. However, in younger patients in whom there is a low risk for surgery, subtotal resection of the adrenal glands should be considered. Nevertheless, it may still be preferable to treat elderly AIMAH patients by conventional radical surgical therapy after obtaining written informed consent to the need for lifelong corticosteroid therapy.

In conclusion, unilateral adrenalectomy should be considered as a treatment option for patients with Cushing’s syndrome due to AIMAH, but it is necessary to closely follow them up for long periods after surgery. Furthermore, bilateral adrenalectomy is indicated in patients with exacerbation of Cushing’s syndrome, but it may increase the risks of undergoing surgery in elderly patients, as in the current case. Therefore, one-stage bilateral adrenalectomy may be the treatment of choice in elderly patients with AIMAH.

The authors state that they have no Conflict of Interest (COI).

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