Bilateral Adrenalectomy with Autotransplantation of Adrenocortical Tissue or Unilateral Adrenalectomy: Treatment Options for Pheochromocytomas in Multiple Endocrine Neoplasia Type 2A

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Abstract. Surgical strategies for pheochromocytomas in patients with multiple endocrine neoplasia (MEN) type 2 syndrome have been controversial. The purpose of this study is to review the current status of patients with MEN 2 who underwent adrenalectomy with or without adrenal autotransplantation. We studied 15 patients with MEN 2A who underwent adrenal surgery between 1981 and 1992. The follow-up survey included physical examination and biochemical determinations. The median period from initial surgery to follow-up was 54 months (range, 0–145 months). Initial bilateral total adrenalectomy was performed on seven patients, and subtotal adrenalectomy was carried out on two. Among six patients who initially underwent unilateral adrenalectomy, four had remained normotensive (median follow-up, 61 months), whereas the other two patients had to undergo reoperation on the contralateral side because of recurrent symptoms. Two patients were suspected of having had a relapse of the disease after total adrenalectomy. Seven patients underwent adrenal autotransplantation; however, none of them were able to discontinue glucocorticoid replacement therapy. In MEN 2A patients having large pheochromocytomas on only one side, unilateral adrenalectomy can be a suitable alternative to bilateral adrenalectomy in terms of blood pressure control and preservation of adrenocortical function. The attempt to preserve adrenocortical function by autotransplantation is discouraged.

Key words: Multiple endocrine neoplasia type 2A, Pheochromocytoma, Adrenalectomy, Autotransplantation of adrenocortical tissue

ALTHOUGH pheochromocytoma is a rare cause of hypertension, it occurs more frequently in a patient with medullary carcinoma of the thyroid and/or parathyroid hyperplasia whose condition is known as multiple endocrine neoplasia type 2 (MEN 2) since Sipple reported the association in 1961 [1]. Multiple pheochromocytomas are believed to be successors of adrenomedullary hyperplasia [2] and occur bilaterally in high frequency (65–72%) [3, 4], but the clinical attitude and the growth rate are different from one another.

Surgical management of the pheochromocytomas in this syndrome has been subject to controversy. van Heerden et al. have recommended an initial bilateral total adrenalectomy as a definite and safe surgical strategy for all the patients with the ailment [5], whereas some have claimed that a unilateral adrenalectomy is an alternative in some patients when the adrenomedullary disease involves only one gland because all hyperplastic glands are not always responsible for the symptoms and the Addisonian state may be
unfavourable [6-8].

Reviewing our experience, we examined the value of unilateral adrenalectomy and bilateral adrenalectomy with adrenal autotransplantation in order to preserve adrenocortical function as treatment options for pheochromocytomas in patients with MEN 2A.

Patients and Methods

Sixteen patients who were members of 8 non-related families with MEN 2A underwent adrenal surgery between 1981 and 1992. One of the patients was excluded from this study because the initial operation for the adrenal glands was carried out at another institution.

The diagnosis of pheochromocytoma was made biochemically (determinations of plasma levels of catecholamines and urinary excretion of catecholamines and/or their metabolites) and radiographically with CT scans and/or $^{131}$I metaiodobenzylguanidine ($^{131}$I MIBG) scans. All of the patients except for one were followed up at our institution. The follow-up study consisted of physical examination (including measurement of blood pressure) and biochemical determinations (metanephrines and normetanephrines in a single voided urine and plasma concentration of cortisol, ACTH, aldosterone and plasma renin activity) on an outpatient basis. The upper limits of the normal ranges of metanephrines (M) and normetanephrines (NM) in a single voided urine are 200 ng/mg creatinine and 300 ng/mg creatinine, respectively. A criterion, defined as a positive result when the $M + NM \geq 1000$, has sensitivity of 88% and specificity of 98% for making a diagnosis of pheochromocytoma [9].

We performed adrenal autotransplantation on 7 patients who underwent bilateral total adrenalectomy. For autotransplantation, a piece of macroscopically normal adrenal tissue was removed from the resected specimen and the adrenomedullary tissue was excised from the piece. After making recipient sites in the thigh of the patients, we sliced the pieces of adrenocortical tissue into small fragments and autoimplanted each fragment into the muscles or beneath the fascia. The total weight of grafted tissue ranged from approximately 1 to 2 g. The adrenocortical tissues for the graft were handled in a cooled physiological saline during the procedure. All patients received glucocorticoid replacement according to schedule.

Results

Eight patients were female with a median age of 35 years (range: 16-58) and seven were male with a median age of 43 years (range: 15-64). All patients showed increased urinary excretion of catecholamines and/or their metabolites, preoperatively. The median duration from the initial operation to follow-up of the patients was 54 months (range 0-145 months).

Size of pheochromocytoma and types of surgery performed

The tumor sizes of pheochromocytomas in the left and right adrenal glands on CT scan at initial operation and the types of surgical treatment for each patient are shown in Fig. 1. The adrenal gland, contralateral to the pheochromocytoma developed, seemed to be normal in size on CT scan in four patients.

Clinical courses of the patients (Figs. 2 and 3)

Initial bilateral (one-stage) total adrenalectomy

![Fig. 1.](image-url) Tumor diameters (mm) of the left and right adrenal glands on CT scan at the initial operation. B, S, U, and C denote patients who underwent the following operations—B, initial bilateral adrenalectomy; S, subtotal adrenalectomy; U, unilateral adrenalectomy; C, contralateral adrenalectomy after the initial operation.
was performed on 7 patients. Five of them were with adrenal autotransplantation and two of them were without the procedure. Hypertension persisted in one patient with the autotransplantation, whereas metanephrines and normetanephrines in a single voided urine have been in the normal ranges. One patient with autotransplantation was suspected of having a local recurrence of the disease in the left adrenal bed, although she did not have hypertension.

Two patients underwent bilateral subtotal adrenalectomy. One of them, who had liver metastasis from medullary thyroid carcinoma, received the adrenal surgery to relieve her symptoms, but she died due to lactic acidosis of unknown etiology a month later. The other patient was treated as a case of sporadic multiple bilateral pheochromocytomas because he had no evidence of MEN 2 at that time [10]. He discontinued the replacement of glucocorticoid a month following surgery and has never experienced adrenal insufficiency. He did not need any

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Fig. 2. Types of adrenalectomy at the initial operation and clinical course of the patients. Open symbols, without adrenal autotransplantation; Solid symbols, with adrenal autotransplantation; Squares, patients who underwent contralateral adrenalectomy (Numbers in parentheses are follow-up months after initial operation). *, hypertension (+); **, patient with liver metastases from medullary thyroid carcinoma; ***, the diagnosis of MEN 2 was made 11 years after the adrenal operation.

Fig. 3. Postoperative determinations of metanephrine (M) and normetanephrine (NM) in a single voided urine. The line in the figure represents M+NM=1000. Open symbols, without adrenal autotransplantation; Solid symbols, with adrenal autotransplantation. *, hypertension (+); adrex., adrenalectomy.
extra-supplementation of glucocorticoid even when he was admitted to the hospital because of ileus. The diagnosis of MEN 2A was made 11 years after the adrenalectomy when the medullary thyroid carcinoma emerged. This patient showed his metanephrine and normetanephrine in a single voided urine within the normal ranges.

Unilateral adrenalectomy was carried out on 6 patients. Two of them underwent adrenalectomy on the contralateral side along with the autotransplantation 18 and 76 months later, respectively (two-stage total adrenalectomy). Both patients had been suffering from hypertension, and one of them was suspected of having a metastasis or an ectopic lesion of pheochromocytoma in the pelvis. Three out of the other four patients were not suffering from hypertension, although the metabolites of catecholamines exceeded the upper limit of the normal ranges (the range of follow-up: 54–72 months, median 67 months). One patient was referred to another hospital after surgery to treat cancer of the tongue, and therefore recent data were not available.

Among the 13 patients whose latest determination of metanephrines (M) and normetanephrines (NM) in a single voided urine were available, both of the measurements were within the normal ranges in five patients, and the sum of the measurements (M + NM) exceeded 1000 in five patients (Fig. 3). Hypertension remained in three patients, though they underwent total adrenalectomy in either one- or two-stage operation.

### Table 1. Determinations of plasma cortisol level, aldosterone concentration, and renin activity after adrenal autotransplantation

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at trpl. / gender</th>
<th>Follow-up after trpl. (months)</th>
<th>PCC</th>
<th>PAC</th>
<th>PRA</th>
</tr>
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<tr>
<td>1</td>
<td>58 / f</td>
<td>76</td>
<td>undetectable</td>
<td>5.4</td>
<td>not determined</td>
</tr>
<tr>
<td>2</td>
<td>22 / f</td>
<td>69</td>
<td>3.3</td>
<td>3.9</td>
<td>0.6</td>
</tr>
<tr>
<td>3</td>
<td>20 / f</td>
<td>63</td>
<td>undetectable</td>
<td>2.3</td>
<td>6.2</td>
</tr>
<tr>
<td>4</td>
<td>22 / f</td>
<td>61</td>
<td>undetectable</td>
<td>3.9</td>
<td>not determined</td>
</tr>
<tr>
<td>5</td>
<td>43 / m</td>
<td>49</td>
<td>undetectable</td>
<td>2.3</td>
<td>7.0</td>
</tr>
<tr>
<td>6</td>
<td>26 / m</td>
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<td>3.1</td>
<td>6.7</td>
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</tr>
<tr>
<td>7</td>
<td>44 / m</td>
<td>13</td>
<td>undetectable</td>
<td>4.3</td>
<td>not determined</td>
</tr>
</tbody>
</table>

Trpl., autotransplantation; PCC, plasma cortisol concentration (normal range: 4.5–24 μg/dl); PAC, plasma aldosterone concentration (normal range: 2.2–15 ng/dl); PRA, plasma renin activity (normal range: 0.5–3.0 ng/ml/h).

Outcome of adrenal autotransplantation

None of the seven patients who underwent adrenal autotransplantation along with initial or completion bilateral total adrenalectomy could discontinue the glucocorticoid replacement therapy (the range of follow-up after the adrenal autotransplantation; 13–76 months). Three patients developed symptoms of adrenal insufficiency despite the replacement. Plasma cortisol was detectable in two patients, although subnormal. The levels of plasma aldosterone concentration (PAC) were within normal range in all the patients (Table 1). Two patients were suspected of having a recurrence of pheochromocytoma; however, $^{131}$I MIBG scan disclosed no evidence of recurrence at the recipient site of the autotransplantation in either of them.

Discussion

The surgical strategies for pheochromocytomas in patients with MEN 2 syndrome have been controversial and there are three treatment options: bilateral total adrenalectomy, bilateral subtotal adrenalectomy, and unilateral adrenalectomy. Although bilateral total adrenalectomy may eradicate the adrenomedullary disease, it necessitates a lifelong glucocorticoid replacement therapy and the risk of adrenal failure. On the other hand, bilateral subtotal adrenalectomy or unilateral adrenalectomy retains adrenocortical function, but the
PHEOCHROMOCYTOMAS IN MEN TYPE 2A

**Disease**

Some surgeons have advocated initial bilateral total adrenalectomy because even the grossly normal adrenal gland always showed adrenomedullary involvement [5, 11]; however, others have expressed a different opinion about the prophylactic removal of a macroscopically normal adrenal at the same time of operation for resecting obvious pheochromocytoma on the other side [6-8]. Tibblin et al. have recommended unilateral adrenalectomy when the largest diameter of the biggest tumor is less than 5 cm and the contralateral side is grossly normal by palpation [6]. Laimore, et al. proposed that the treatment of choice for patients with unilateral pheochromocytoma is resection of only the involved gland [8].

In our series, six patients underwent unilateral adrenalectomy, and five of them were followed-up at our institution. Their contralateral adrenal gland was saved for from 18 to 76 months (median 67 months). Unilateral adrenalectomy can be an alternative as a measure for preserving adrenocortical function when the patient has an adrenal tumor on only one side or he/she has a large tumor on one side with a small one on the other side. The decision depends on the definition of utility in the treatment options and other information such as patient’s age, co-morbidity, possibility of pregnancy in the future and family history of cerebrovascular disease. Bilateral subtotal adrenalectomy can also preserve adrenocortical function [12] as in one of the patients in this report, but reoperation may be difficult and hazardous when the recurrence occurs around the adrenal bed.

One of our patients was suspected of having a metastasis or an ectopic recurrence of pheochromocytoma. Some authors have no experience of malignant pheochromocytomas [6, 7]; however, van Heerden et al. reported 3 cases of metastatic pheochromocytoma in their 17 patients [5], and there is another report of a malignant case [13]. Thompson et al. detected metastatic pheochromocytomas in 2 out of 8 patients with MEN 2A using 131I MIBG scans [14]. Oishi et al. reviewed 82 cases of MEN 2 from the Japanese literature and reported that metastatic pheochromocytoma had been seen in four (4.8%) [4].

In this study, four patients showed higher levels of metanephrine (MN) and normetanephrine (NMN) in a single voided urine (i.e. MN + NMN ≥ 1000) even though their adrenal glands were totally removed. Although the reasons for false positive results also needed to be considered [15, 16], two of them were suspected of having recurrences.

We carried out adrenal autotransplantation aiming to preserve adrenocortical function because acute adrenal insufficiency seems to be a crucial problem after bilateral total adrenalectomy. Laimore et al. experienced the crisis in 10 of 43 patients (23%) [8], whereas van Heerden et al. reported that there was no major problem due to adrenal absence in their series [5]. Among the nine patients who underwent one- or two-stage total adrenalectomy, we have tried autotransplantation of adrenal tissue on seven patients. Yet, none of them were free from glucocorticoid replacement, and three of them developed adrenal failure. Successful adrenal autotransplantation has been reported in patients with Cushings’ disease [17, 18]. The attempt has also been made in patients with MEN 2, though there are few reports of success [19, 20]. As for the producing glucocorticoid, the amount of autografted tissue in our series might be insufficient because the levels of the glucocorticoid secreted depend on the amount [21]. Nevertheless, all of the seven patients showed that their levels of plasma aldosterone concentration were in the normal range, and there were no patients who needed to take the replacement therapy of mineralocorticoid. This finding may indicate that the cells of zona glomerulosa in autografted adrenocortical tissue regenerate and secrete mineralocorticoid aldosterone. Yet, a hypothesis that the cells in the zona fasciculata and the zona reticularis develop and grow from the cells in the zona glomerulosa just beneath the adrenal capsule is unlikely to be true in human beings as opposed to the findings obtained from experiments with animals [22, 23]. This can be explained by the suppression of endogenous ACTH secretion from the pituitary gland during the early post-operative period due to a relatively large amount of glucocorticoid supplementation to prevent adrenal failure [21, 24].

In clinical settings, the amount of adrenal tissue available for autografting is usually small because of the large pheochromocytoma. In addition, the fate of the medullary tissue after the autotransplantation is not clear, although we have not experienced recurrence of pheochromocytomas from the autograft. Several investigators have claimed that the medullary tissue did not regener-
ate based on experiments [21-25] and on clinical observations [17, 26]. To the contrary, there are a few articles showing opposite findings from experiments [27, 28] and reports of performing autotransplantation of adrenal medulla successfully to relieve the symptoms in patients with Parkinson’s disease [29, 30]. For these reasons, we should conclude that the attempt of adrenal autotransplantation to preserve adrenocortical function is discouraged in patients with MEN 2A.

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