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CASE REPORT

Unilateral adrenalectomy partially improved hyperglycemia in a patient with primary bilateral macronodular adrenal hyperplasia

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Abstract

Primary bilateral macronodular adrenal hyperplasia (PBMAH) is characterized by bilateral multiple adrenal macro-nodules that often cause mild over-secretion of cortisol in the form of subclinical Cushing's syndrome. We herein describe a case, wherein unilateral adrenalectomy partially improved hyperglycemia in a patient with PBMAH and suggest the usefulness and limitations of this surgical strategy. A 64-year-old woman with type 2 diabetes had an incidental diagnosis of bilateral adrenal lesions. She had a family history of type 2 diabetes, and her HbA1c level was 8.9% under insulin therapy. She did not present with any symptoms associated with Cushing's syndrome. The basal cortisol level was in the normal range (12.0 μg/dL); however, the adrenocorticotropic hormone (ACTH) level was suppressed (2.1 pg/mL) and the serum cortisol level was not suppressed in the dexamethasone test. Computed tomography and magnetic resonance imaging showed bilateral adrenal macro-nodules and ^{131}I-adosterol accumulated in the bilateral adrenal lesions. Collectively, she was diagnosed with subclinical Cushing's syndrome due to PBMAH complicated with diabetes mellitus, hypertension, and dyslipidemia. Laparoscopic left adrenalectomy was performed, and the pathologic findings were consistent with PBMAH. After unilateral adrenalectomy, serum cortisol levels decreased, and hypertension improved. Both HbA1c levels and insulin requirement also decreased, but insulin therapy was continuously needed. It should be noted that hyperglycemia may not be cured after successful surgery in a patient with PBMAH. Additional operation or medical therapy should be considered if unilateral adrenalectomy is unable to correct hypercortisolism in PBMAH patients.

Keywords Primary bilateral macronodular adrenal hyperplasia (PBMAH) · Type 2 diabetes · Glucocorticoid-induced diabetes · Subclinical Cushing's syndrome · Unilateral adrenalectomy

Introduction

Primary bilateral macronodular adrenal hyperplasia (PBMAH) is characterized by the presence of bilateral multiple adrenal macro-nodules [1, 2]. PBMAH often causes mild over-secretion of cortisol in the form of subclinical Cushing's syndrome, which is usually detected as an adrenal incidentaloma. This disease was formerly called adrenocorticotropic hormone (ACTH) independent macronodular adrenal hyperplasia (AIMAH); however, currently, it is called PBMAH, because ectopic ACTH production in the adrenal glands itself could induce the development of bilateral adrenal hyperplasia and nodular lesions [3]. Additionally, aberrantly expressed G-protein-coupled receptors, such as glucose-dependent insulinotropic peptide (GIP), catecholamine, vasopressin, serotonin and angiotensin II receptors, were often observed in the adrenal lesions of PBMAH [1, 2]. PBMAH usually occurs sporadically, but somatic or germline mutations of armadillo repeat containing 5 (ARMC5) are evident in almost half of the cases [4, 5].

The standard therapy for typical adrenal Cushing's syndrome, including the causative cortisol-producing adenoma, is unilateral adrenalectomy [6, 7]. Unilateral adrenalectomy is also applied for treating cortisol over-secretion due to PBMAH, because this approach restores cortisol

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over-secretion and improves metabolic complications such as diabetes mellitus, hypertension, and dyslipidemia [8, 9]. One-sided operation on PBMAH is also useful to avoid the risk of life-threatening adrenal crisis when compared with bilateral adrenalectomy, which requires lifelong hydrocortisone replacement. Long-term observational data indicate that unilateral adrenalectomy should be performed for PBMAH with mild cortisol excess [10].

We herein describe a case, wherein unilateral adrenalectomy decreased cortisol levels and partially improved hyperglycemia in a patient with PBMAH. We also suggest the usefulness and limitations of this surgical strategy for treating hyperglycemia in PBMAH.

Case report

A 64-year-old woman with type 2 diabetes had an incidental diagnosis of bilateral adrenal lesions. She was diagnosed with type 2 diabetes at the age of 53 years and started insulin therapy 4 years later. Her mother and elder brother also had type 2 diabetes. Family history of hypercholesterolemia could not be confirmed.

Her body weight and body mass index were 57.6 kg and 23.6 kg/m^2, respectively. Her systolic and diastolic blood pressures were 140 and 86 mmHg under antihypertensive medications (amlodipine 5 mg, olmesartan 20 mg and carvedilol 10 mg), respectively. She had no symptoms suggestive of Cushing's syndrome. Complete blood count, liver function, renal function, and electrolytes were within the normal range. The fasting plasma glucose level was 149 mg/dL, and HbA1c was 8.9% under insulin therapy (48 units per day) and anti-diabetic medications (metformin 500 mg, pioglitazone 7.5 mg and voglibose 0.9 mg). Fasting c-peptide immunoreactivity (CPR) was 2.13 ng/mL, c-peptide index (CPI) was 0.93, and anti-GAD antibody was negative. Mild diabetic microangiopathies were evident (simple retinopathy, early nephropathy with microalbuminuria and neuropathy with foot numbness). The low-density lipoprotein cholesterol level was 138 mg/dL, triglyceride level was 94 mg/dL, and high-density lipoprotein cholesterol level was 82 mg/dL under treatment (rosuvastatin 2.5 mg). Endocrine data showed that the serum cortisol level was within the normal range (12.0 µg/dL), the diurnal rhythm disappeared, and urinary free cortisol levels increased (131 µg/day). Morning plasma ACTH level was suppressed (2.1 pg/mL), and serum cortisol levels were not suppressed after the dexamethasone test (cortisol 12.7 µg/dL after a 1-mg dose; 10.6 µg/dL after an 8-mg dose), indicating autonomous cortisol production in the adrenal lesion and relatively high cortisol levels close to overt Cushing's syndrome. Levels of aldosterone and catecholamines were in the normal range. Endocrine tests to investigate aberrant receptor expression in PBMAH were not performed because of patient's request. Computed tomography and magnetic resonance imaging showed bilateral adrenal macro-nodules (Fig. 1), and these sizes were 3.2 × 2.6 × 4.2 cm (18.3 cm^3) in the right side and 2.2 × 4.2 × 6.5 cm (31.4 cm^3) in the left side. These CT values were 15.0 HU in the right side and 15.7 HU in the left side. ^{131}I-adosterol accumulated in the bilateral adrenal lesions with no laterality. Osteoporosis was not evident in the bone density test. Collectively, she was diagnosed with subclinical Cushing's syndrome due to PBMAH complicated with diabetes mellitus, hypertension, and dyslipidemia [11].

Insulin therapy was continued, and anti-diabetic medications were discontinued to simplify the diabetic treatment on initial admission. We considered the cause of her hyperglycemia to be composed of two factors: one was type 2 diabetes and the other was glucocorticoid-induced diabetes. Almost 1 year later, she agreed to undergo adrenal surgery in the hope of improving glucocorticoid-induced diabetes. For preoperative treatment, intensive insulin therapy was initiated (72 units per day), and her glycemic control improved. Laparoscopic left adrenalectomy was performed, because the left side nodules were dominant. The resected adrenal nodules were huge (7.5 × 4.0 × 2.0 cm size), and pathological examination showed micro-adenomatous hyperplasia of the surrounding zona fasciculata, which were consistent with PBMAH (Fig. 1). After unilateral adrenalectomy, serum cortisol levels decreased (6.7 µg/dL), and the urinary free cortisol level was normalized (55 µg/day). However, ACTH was low (3.4 pg/mL) in the morning and cortisol was relatively high (5.5 µg/dL) at night, indicating that mild cortisol excess remained after surgery. Hypertension clearly improved, and the use of major antihypertensive drugs (amlodipine and olmesartan) was stopped 6 months after surgery. Both HbA1c levels and insulin requirement (before surgery: 72 units, after surgery: 48 units) also decreased, but insulin therapy was continuously needed (Fig. 2). Body weight also decreased possibly due to cortisol reduction, which gradually returned to the original levels with no alterations in glycemic control. The patient adhered to the diet moderately throughout the clinical course but did not perform exercise because of foot numbness. Fasting CPR (1.49 ng/mL) and CPI (0.97) did not change after surgery. Statin therapy for dyslipidemia continued.

Discussion

Endogenous Cushing's syndrome or subclinical Cushing's syndrome is accompanied with numerous metabolic complications including hypertension, diabetes, dyslipidemia, and osteoporosis [6, 7]. Persistent glucocorticoid excess can induce insulin resistance and impaired insulin secretion, leading to secondary diabetes. Glucose abnormalities

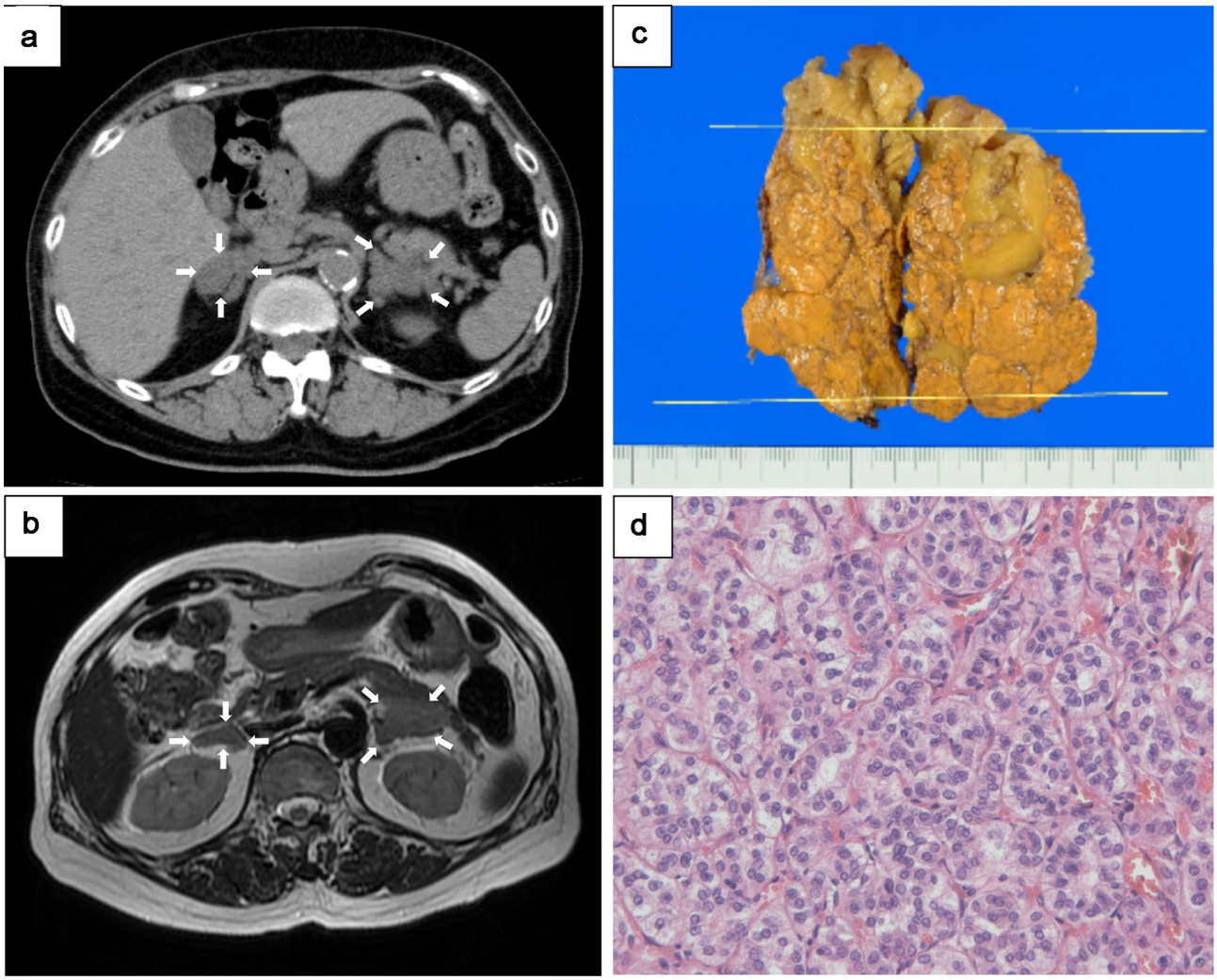

Fig. 1 Computed tomography image (**a**) and magnetic resonance imaging T2-weighted image (**b**) of bilateral adrenal lesions (white arrow) in the present case. Note that the left side nodules are clearly dominant. Gross-cut surfaces of the resected left adrenal nodules show a huge mass-like lesion (7.5×4.0×2.0 cm size) (**c**). Pathological examination of the resected nodules shows micro-adenomatous hyperplasia of the surrounding zona fasciculata (×200 magnification, hematoxylin and eosin staining) (**d**), which were consistent with primary bilateral macronodular adrenal hyperplasia

including diabetes mellitus and impaired glucose tolerance in endogenous Cushing's syndrome account for 43–83% of all complications [12], and glucocorticoid-induced diabetes could contribute to the risk of mortality in patients with Cushing's syndrome [13]. We considered that the main cause of hyperglycemia in the present case was type 2 diabetes according to the clinical course and family history. HbA1c levels partially improved after surgery, supporting the idea that glucocorticoid-induced diabetes due to subclinical Cushing's syndrome with PBMAH was an exacerbation factor of hyperglycemia. While hypertension improved, but dyslipidemia did not after surgery, suggesting that the latter could be caused by diabetes mellitus or familial hypercholesterolemia rather than Cushing's syndrome.

Glucocorticoid is one of the hormones with an antagonistic action to insulin, and glucocorticoid-induced hyperglycemia occurs during the postprandial period when glucocorticoids exert anti-insulin effects in the liver, skeletal muscle, and adipose tissue. Insulin inhibits gluconeogenesis and glycogenolysis in the liver and increases glucose uptake in the muscle and fat. In contrast, glucocorticoid excess could interfere with all these effects, leading to the development of insulin resistance [12, 14, 15]. Glucocorticoid excess also increases hepatic glucose production by inducing gluconeogenesis enzymes including glucose-6-phosphatase, which could cause glucose abnormalities under the fasting state. Insulin resistance due to persistent glucocorticoid excess leads to hyperinsulinemia in the early phase, and impaired insulin secretion appears later through reduced expression

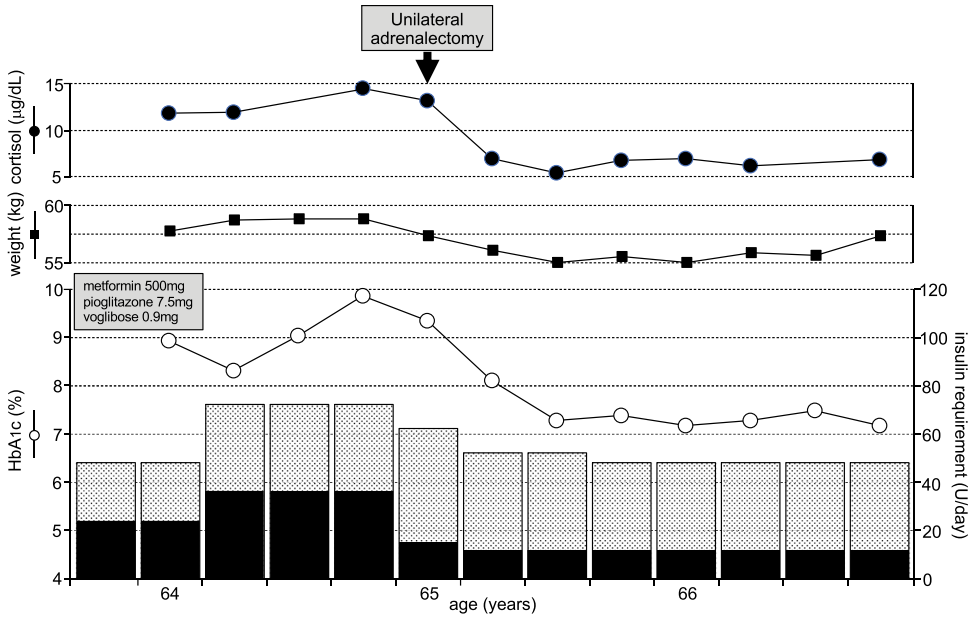

Fig. 2 Clinical course of the patient in the present case. Serum cortisol level, body weight, HbA1c, and the total dose of insulin requirement are indicated by closed circles, closed squares, open circles, and bar chart, respectively. Black bars represent the daily requirement of long-acting insulin, and hatched bars represent the daily requirement of rapid-acting insulin. After unilateral adrenalectomy, both HbA1c levels and insulin requirement decreased with reduction in the cortisol level. The patient's body weight also decreased and gradually returned to the original levels, with no alterations in glycemic control

of glucose transporter 2 (GLUT2) and glucokinase [12, 14, 15]. In the present case, insulin requirement decreased without anti-diabetic medications after surgery, supporting the idea that glucocorticoid-induced insulin resistance improved with restoration of hypercortisolism. Mild weight loss, possibly due to cortisol reduction, was considered as an additional factor that decreases insulin requirement. Although it's unclear why the requirement of long-acting insulin decreased but rapid-acting insulin did not, it's possible that diet-induced hypercortisolism remained in residual adrenal lesion due to aberrant expression of GIP receptor [1, 2]. Fasting CPR and CPI did not improve 6 months after the operation, suggesting that type 2 diabetes, rather than glucocorticoid-induced diabetes, might have caused β cell dysfunction.

For patients with exogenous glucocorticoid-induced hyperglycemia, medical treatment should include insulin therapy and drugs that improve insulin sensitivity (metformin) and postprandial insulin secretion (dipeptidyl peptidase 4 inhibitors: DPP4 inhibitors, glucagon-like peptide 1 analogues: GLP1 analogues, and sulfonylureas). Thiazolidinediones are not recommended as first-line treatment, because they may increase the risk of heart failure and bone loss in Cushing's syndrome [12]. Anti-diabetic therapy in patients with hyperglycemia due to endogenous Cushing's syndrome has not been explored, and insulin therapy is often used for glycemic control, especially in preoperative treatment [12]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have not been described in the literature for the treatment of glucocorticoid-induced diabetes, but they may easily cause ketosis in Cushing's syndrome, because glucocorticoids have anti-insulin effects and induce lipolysis in the adipose tissue [12, 14, 15].

Unilateral adrenalectomy on PBMAH has been applied as a therapeutic approach because of lower frequency of complications than that with bilateral adrenalectomy [8, 9]. Although, deciding which side to remove, is not simple, the larger gland is usually excised in the hope of restoring the hypercortisolism. Initial remissions are reported in more than 90% of cases, and glucocorticoid-related complications including diabetes improve. A major concerning issue of unilateral adrenalectomy is that contralateral adrenalectomy might be necessary in the future due to recurrence of hypercortisolism. Recently, long-term observational data indicate that unilateral adrenalectomy leads to clinical remission and a lower incidence of adrenal crisis but in less sufficient biochemical control of hypercortisolism [10]. Unilateral adrenalectomy should be performed for PBMAH with asymmetric hyperplasia or mild cortisol secretion [10, 16, 17]. Glucocorticoid-induced diabetes is sometimes cured by surgical treatment in overt Cushing's syndrome. In the present case, however, insulin therapy was continuously needed after the restoration of glucocorticoid excess. It is not easy to predict which component (type 2 diabetes or glucocorticoid-induced diabetes) is the main factor that induces hyperglycemia before surgery, and it should be noted that hyperglycemia may not be cured after successful surgery in a patient with PBMAH. In terms of mortality, surgical improvement of Cushing's syndrome reduces cardiovascular risk when compared with conservative treatment [18], which may be applied in the present case.

If hypercortisolism appears after unilateral adrenalectomy on PBMAH, medical therapy or additional operation should be considered. Several medical treatments are available for endogenous Cushing's syndrome to improve glucocorticoid excess. Metyrapone is a potent inhibitor

of the steroidogenesis enzyme 11β-hydroxylase, which is often prescribed for the medical treatment of Cushing's syndrome [12, 19]. Ketoconazole and mitotane are other choice for steroidogenesis inhibitors, but the latter is suitable for adrenocortical carcinoma because of its adrenolytic effects. Mifepristone is a glucocorticoid receptor antagonist that can be effective in patients with glucocorticoid excess due to PBMAH [20], but this drug was not authorized in several countries including Japan. Furthermore, there are potential treatments targeting the aberrant receptors expressed in PBMAH nodules, such as octreotide, propranolol or angiotensin II receptor antagonist for PBMAH associated with GIP receptors, adrenalin receptors or angiotensin II receptors, respectively [1, 2].

In conclusion, this is a case of unilateral adrenalectomy in a patient with PBMAH and partially improved hyperglycemia, but insulin therapy was continuously needed after the restoration of glucocorticoid excess. It should be noted that hyperglycemia may not be cured after successful surgery in a patient with PBMAH. This surgical strategy is useful, but the application of this treatment should be decided carefully on a case-by-case basis. Additional operation or medical therapy should be considered if unilateral adrenalectomy does not correct hypercortisolism in PBMAH.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard This article does not contain any studies with human or animal subjects performed by any of the authors.

Informed consent The identity of the patients was protected. The patient provided informed consent for this study.

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