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The Potential of Computed Tomography Volumetry for the Surgical Treatment in Bilateral Macronodular Adrenal Hyperplasia: A Case Report

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Although adrenal resection is a major option to control hypercortisolemia in patients with bilateral macronodular adrenal hyperplasia, a predictive method for postoperative cortisol production has not been established. A 53-year-old man with ulcerative colitis was referred to our hospital for bilateral multiple adrenal nodules and hypertension. Physical and endocrinological examination revealed inappropriate cortisol production and suppressed secretion of adrenocorticotropic hormone with no typical signs of Cushing's syndrome. Imaging analysis revealed bilateral adrenal nodular enlargement, the nodules of which had the radiological features of adrenocortical adenomas without inter-nodular heterogeneity. In addition, computed tomography volumetry demonstrated that the left adrenal gland (70 mL) accounts for three quarters of the total adrenal volume (93 mL). The patient was diagnosed as subclinical Cushing's syndrome due to bilateral macronodular adrenal hyperplasia, and subsequently underwent a left laparoscopic adrenalectomy with the estimation of 75% decrease in the cortisol level based on the adrenal volume. The surgical treatment ultimately resulted in control of the cortisol level within the normal range, which was compatible to our preoperative prediction. However, regardless of the sufficient cortisol level, ulcerative colitis was exacerbated after the surgery, which needed a systemic therapy for remission. This case indicates successful surgical control of hypercortisolemia based on computed tomography volumetry in bilateral macronodular adrenal hyperplasia, as well as the perioperative exacerbation risk for inflammatory diseases in Cushing's syndrome. We report the potential utility of computed tomography volumetry as a quantitative method with retrospective evaluation of our historical cases.

Keywords: bilateral macronodular adrenal hyperplasia; computed tomography volumetry; Cushing's syndrome; hypertension; ulcerative colitis
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Introduction

Bilateral macronodular adrenal hyperplasia (BMAH) is a rare cause of Cushing's syndrome (CS), accounting for less than 2% of all the causes (Newell-Price et al. 2006). Most reported cases were sporadic, but up to 25% of them have been reported to harbor germline mutations of a tumor suppressor gene, *armadillo repeat containing 5* gene (Espiard et al. 2015). In the pathogenesis of BMAH, para-secretion of adrenocorticotropic hormone (ACTH) from its

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nodules causes hyperplastic adrenal glands, resulting in cortisol overproduction independently from pituitary ACTH secretion (Louiset et al. 2013). BMAH tends to have milder hypercortisolemia than the other etiologies of CS (Lacroix 2009). Therefore, the majority of patients with BMAH present no specific physical features and diagnosed as subclinical CS. However, subclinical CS also harbors the increased prevalence of diabetes and hypertension similar to overt adrenal CS (Tauchmanovà et al. 2002; Morelli et al. 2017). In addition, several studies have reported that subclinical CS could be a risk factor for not only cardiovascular disease but also mortality (Tauchmanovà et al. 2002; Morelli et al. 2017; Patrova et al. 2017). An adrenalectomy for adrenal subclinical CS, therefore, plays a pivotal role to improve the prognosis. In a typical adrenal CS case due to a cortisol-producing adrenocortical adenoma, surgical removal of the ipsilateral adrenal gland results in its remission, and endogenous cortisol secretion is maintained by the contralateral adrenal gland. In contrast, a BMAH case needs to consider two aspects of endogenous cortisol secretion in surgical treatment because of the enlarged bilateral adrenal glands as the cause of hypercortisolemia: control of hypercortisolemia and maintenance of the required amount of cortisol production to live. Previous reports have shown their surgical strategies for BMAH based on findings of NP-59 scintigraphy, adrenal vein sampling and the size of adrenal glands (Shinojima et al. 2001; Lamas et al. 2002; Young et al. 2008; Tanaka et al 2019). Although particularly NP-59 scintigraphy has been reported as useful in decision of the surgical treatment (Papierska et al. 2015), those findings are inconclusive for prediction of the postoperative cortisol level due to an insufficient resolution for small lesions under 1.5 cm (Mansoor et al. 2002).

Here, we report a male case of BMAH associated with ulcerative colitis (UC), which is one of chronic inflammatory diseases. In this case, computed tomography (CT) volumetry of the enlarged adrenal glands was employed to predict the extent of decrease in endogenous cortisol production after a unilateral laparoscopic adrenalectomy. We successfully performed a left laparoscopic adrenalectomy which led to improvement of hypercortisolemia with no episode of adrenal insufficiency as expected. However, regardless of the sufficient cortisol level, the patient realized exacerbation of abdominal symptoms related to UC, which required medical management to achieve remission. This case report indicates the utility of CT volumetry in the surgical treatment of BMAH, as well as the perioperative risk for aggravation of inflammatory diseases during the surgical period in subclinical CS.

Case Presentation

A 53-year-old man was referred to our hospital for the evaluation of bilateral adrenal masses, which were detected on abdominal CT as a screening test for secondary hypertension. The patient had a 3-year history of untreated hypertension with no familial episode of hypertension or endocrine disorders. The patient also had received medical therapy, including budesonide, mesalazine and ramosetron, for UC for 5 years. Clinical parameters on admission were as follows: height, 162.0 cm; weight, 65.6 kg; body mass index, 25.33 kg/m^2; blood pressure, 160/107 mmHg under nifedipine of 20 mg/day; heart rate, 94 beats/minute, a normal sinus rhythm. The patient complained about general fatigue, weight gain and edema in both legs. Physical examination revealed mild facial edema and pitting edema in the lower limbs with infectious folliculitis, but no Cushingoid features.

The laboratory data showed a suppressed plasma ACTH level and an inappropriate serum cortisol level with loss of a diurnal rhythm (Table 1, Fig. 1). The urinary cortisol level also elevated and both 1 and 8 mg dexamethasone suppression tests demonstrated non-suppressed serum cortisol levels. In addition, the ACTH level did not respond to corticorelin (synthetic human corticotropin-releasing hormone) injection. Therefore, his endocrinopathy was clinically confirmed as subclinical CS. Stage 2 hypertension and osteoporosis were also diagnosed as complications of subclinical CS, whereas he had minor damages in other organs and no diabetes. Subsequently, abdominal CT revealed multiple nodular enlargement of both adrenal glands. Unenhanced CT showed homogenously hypodense adrenal glands. (lower than 10 Hounsfield unit, Fig. 2A). Contrast-enhanced CT showed weak heterogenous increasement of CT values with rim enhancement in both adrenal glands (Fig. 2B, C). In magnetic resonance imaging, adrenal glands were hypointense compared with the liver on T1-weighted images and were hyperintense on T2-weighted images. At chemical-shift imaging, the adrenal nodules uniformly decreased signal intensity in out-of-phase imaging (Fig. 2D, E). Additionally, fluorodeoxyglucose positron emission tomography/computerized tomography (FDG-PET/CT) images revealed similar FDG uptake among the bilateral nodules (standardized uptake value max, 3.4-3.9) (Fig. 2F). Those findings of morphological evaluation above were compatible with BMAH. In terms of UC, a lower gastrointestinal endoscopy found mild changes of the mucosa: granular appearance, small erosions and loss of vascular markings, limited in the rectum. The clinical severity of UC was also classified as mild based on several physical parameters, including his defecation frequency and vital signs.

Adrenalectomy was required for his complications related to subclinical CS. On the other hand, we also assumed that the patient has an additional risk for exacerbation of UC due to a dramatic change of the endogenous cortisol level after the surgery. Therefore, we employed CT volumetry to calculate the volume of each adrenal gland for preoperative estimation of the surgical effect on cortisol production. CT volumetry was performed based on 1 mm slices of CT images, using a semi-automatic protocol of Ziostation2 version 2.4.2.0.a, a computer software for the volumetry. In this case, CT volumetry indicated a clear dif-

Table 1. Baseline laboratory parameters of the patient.

<Blood>				**<Endocrine>**			
			Reference				Reference
White blood cell	4,600	/μL	3,300-8,600	ACTH	1.7	pg/mL	7-63
Hemoglobin	12.3	g/dL	13.7-16.8	Cortisol	11.6	μg/dL	4.5-21.1
Platelet	37.5	$\times 10^4/\mu L$	15.8-34.8	PRA	2.4	ng/mL/hr	0.3-2.9
AST	18	IU/L	13-30	PAC	10.3	ng/dL	3-16
ALT	12	IU/L	10-42	ARR	4.3		< 20
γ-GTP	43	IU/L	13-64	LH	2.97	mIU/mL	0.1-8.7
Sodium	140	mM	138-145	FSH	7.13	mIU/mL	0.3-13.8
Potassium	4.5	mM	3.6-4.8	DHEA-S	261	ng/mL	380-3,130
Chloride	103	mM	101-108	Testosterone	189	ng/dL	192-884
Albumin	4.0	g/dL	4.1-5.1				
Urea nitrogen	15	mg/dL	8-20	**<24-hour collecting urine>**			
Creatinine	0.62	mg/dL	0.65-1.07	Aldosterone	5.8	μg/day	< 10
Hemoglobin A1c	6.4	%	< 6.5	Cortisol	396	μg/day	80-355
Fast blood glucose	100	mg/dL	73-109				

AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma-glutamyl transferase; ACTH, adrenocorticotropic hormone; PRA, plasma renin activity; PAC, plasma aldosterone concentration; ARR, aldosterone-to-renin ratio; LH, luteinizing hormone; FSH, follicle-stimulating hormone; DHEA-S, dehydroepiandrosterone sulfate.

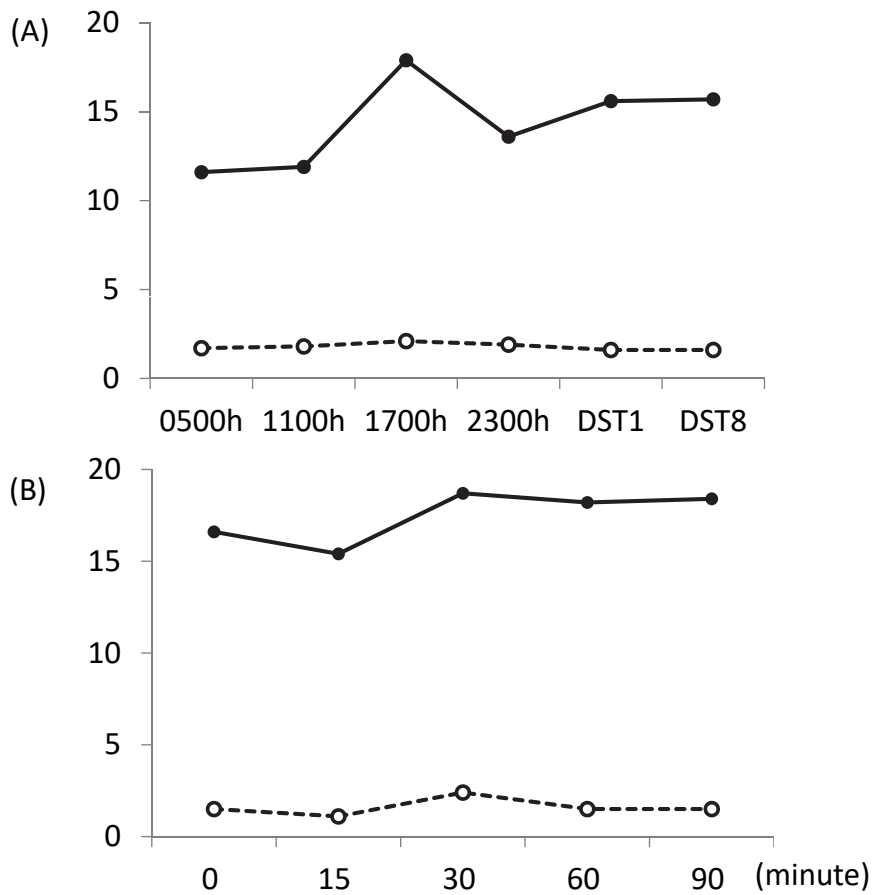

Fig. 1. Secretion dynamics of ACTH and cortisol.
The solid and broken lines indicate cortisol (μg/dL) and ACTH levels (pg/mL), respectively. (A) The circadian rhythm and the results of both DST1 and DST8. Cortisol was not suppressed by dexamethasone loading. (B) The result of the CRH stimulation test. ACTH did not respond to CRH injection.
ACTH, adrenocorticotropic hormone; DST1 and 8, 1 and 8 mg dexamethasone suppression tests; CRH, corticotropin-releasing hormone.

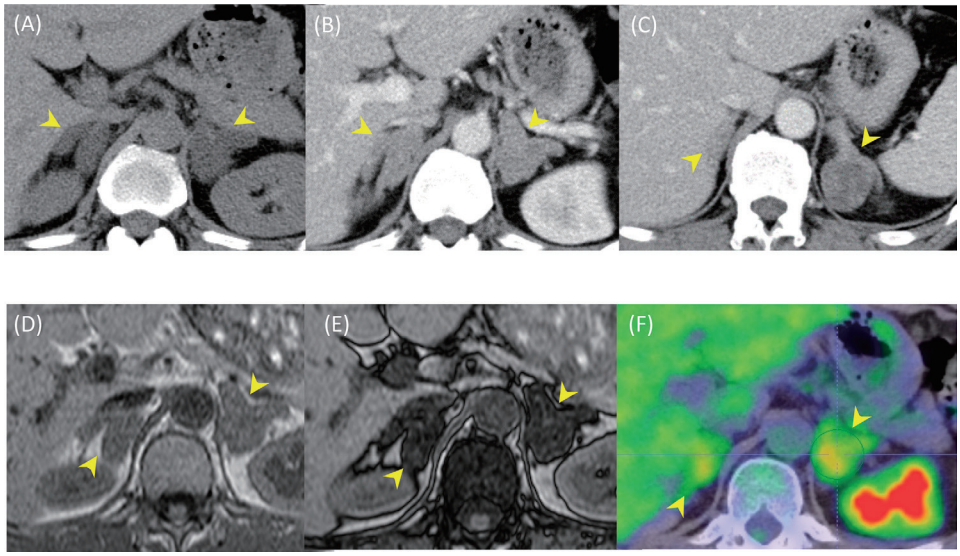

Fig. 2. Imaging analysis on adrenal glands.
A: Plane CT. Arrow heads indicate enlarged adrenal glands.
B&C: Contrast-enhanced CT at venous phase. Both images show adrenal glands at different levels.
D&E: MRI (T1W1) in phase and out of phase, respectively. These images show apparent decrease in signal intensity at both adrenal glands.
F: ^{18}F-FDG-PET/CT. Both adrenal glands show similar standardized uptake value. The standardized uptake value max is within 3.4-3.9.
CT, computed tomography; MRI, magnetic resonance imaging; ^{18}F-FDG-PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computerized tomography.

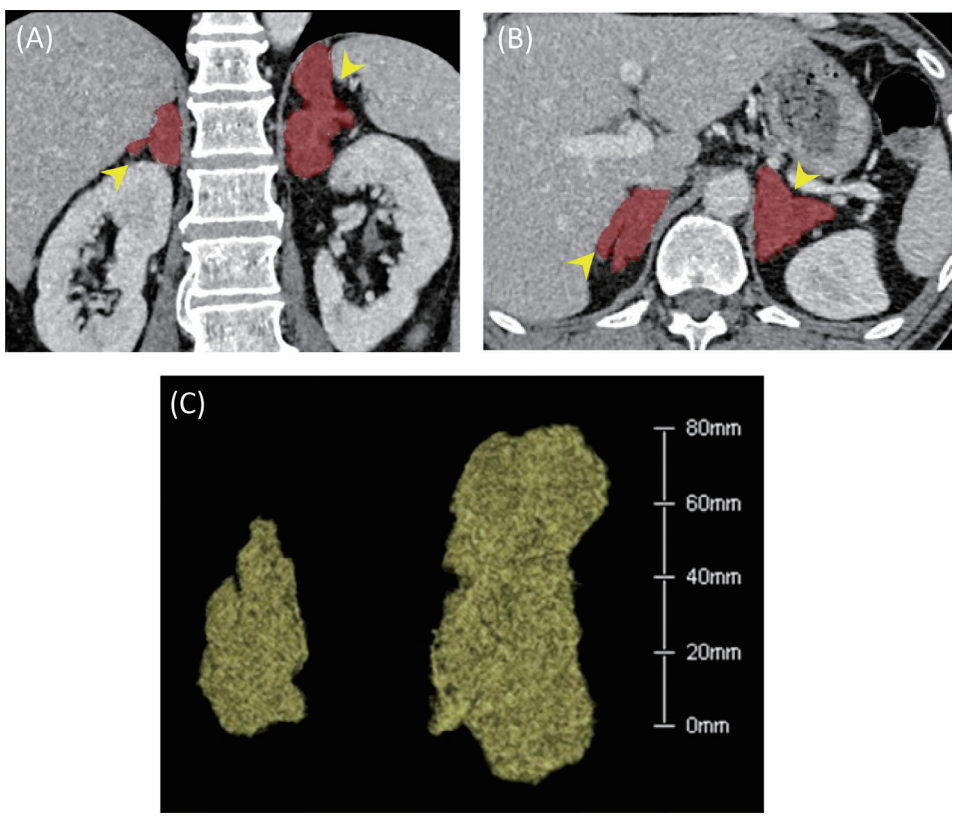

Fig. 3. Calculation of the volume of adrenal glands.
A&B: CT volumetry. Bilateral adrenal glands are marked as red for calculation.
C: The shapes of adrenal glands constructed by CT volumetry. The volume of left and right adrenal glands is estimated as 70 and 23 mL, respectively.
CT, computed tomography.

ference in the volume between the right and left adrenal glands, and the right and left adrenal glands accounted for 24.7% (23 mL) and 75.3% (70 mL) of total adrenal volume (93 mL), respectively (Fig. 3A-C). Considering the internodular homogeneity in imaging analysis, we predicted that removal of a left adrenal could decrease his endogenous cortisol production by 75% and keep the urinary cortisol level within the normal range without adrenal insufficiency. Based on the estimation, the patient underwent a total left laparoscopic adrenalectomy under spironolactone of 50 mg/day, furosemide of 20 mg/day and nifedipine of 40 mg/day as treatment for hypertension (Table 2).

The resected adrenal gland weighed 80 g and measured 100 × 60 × 35 mm (Fig. 4A). Macroscopically, multiple nodules were identified throughout the resected left adrenal cortex. Histological examination revealed that those adrenocortical nodules above were mainly composed of clear cells admixed with intervening foci or island of

Table 2. Changes of clinical parameters during the perioperative period.

	At diagnosis	Before operation	POD 7	POD 37
ACTH (pg/mL)	1.7	2.2	2.8	4.4
Cortisol (μg/dL)	11.6	15.7	6.5	12.8
Urinary cortisol (μg/day)	396	364	134	N/A
Blood pressure (mmHg)	160/107	140/91	128/78	100/71
AHT (n)	1	3	3	3

POD, postoperative day; ACTH, adrenocorticotropic hormone; AHT, antihypertensive agents; N/A, not available.

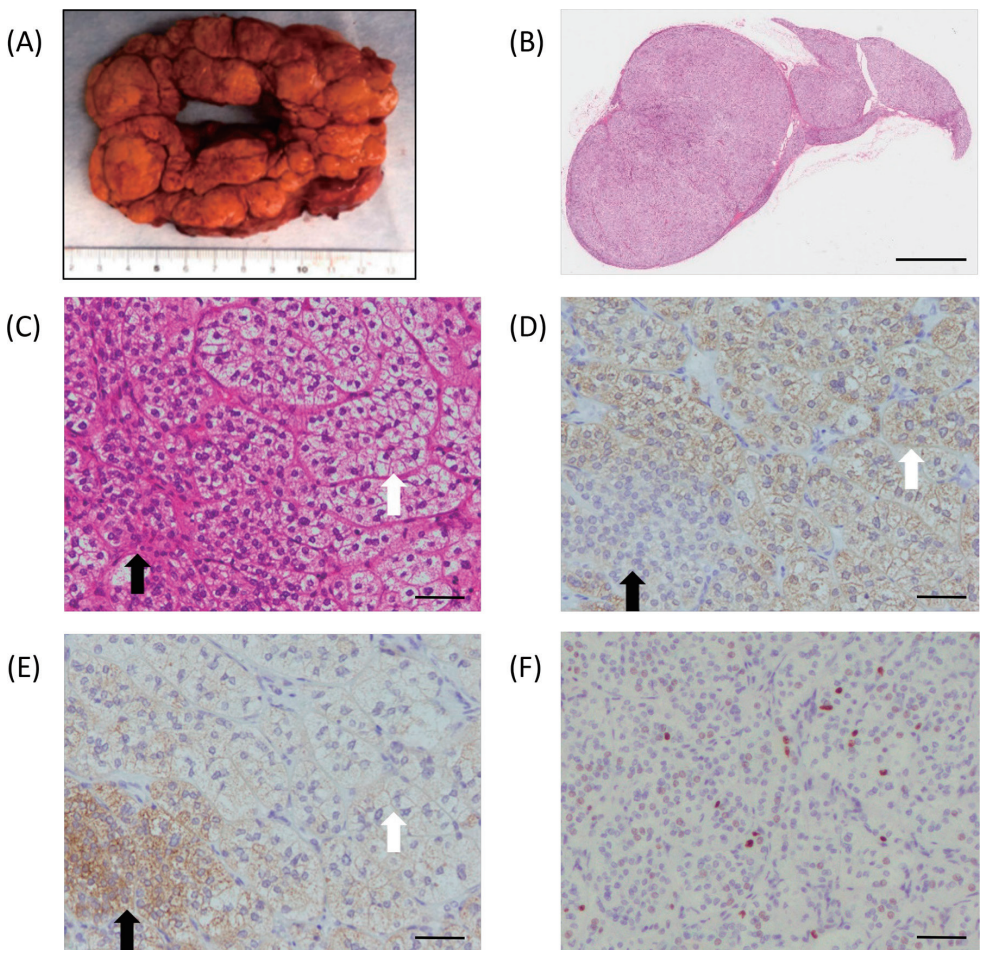

Fig. 4. Pathohistological images of the resected adrenal gland.
(A) Macroscopic view of the left adrenal gland. (B) Hematoxylin and eosin staining (original magnification × 40). (C) Hematoxylin and eosin staining (original magnification × 200). (D) 3β-hydroxysteroid dehydrogenase expression (original magnification × 200). (E) 17α-hydroxylase expression (original magnification × 200). (F) Ki-67 expression (original magnification × 200). Black and white arrows point clear cells and compact cells, respectively. Black bars indicate 5 mm in B and 100 μm in C-F.

compact cortical cells (Fig. 4B, C). Subsequent immunohistochemical examination revealed its unique pattern of steroidogenic enzymes' immunolocalization in individual cell subtypes in the nodules. That is, clear cells were generally positive for 3β-hydroxysteroid dehydrogenase but negative for 17α-hydroxylase, while the compact cells were generally positive for 17α-hydroxylase but negative for 3β-hydroxysteroid dehydrogenase (Fig. 4D, E). Ki-67 labeling index was 4% at the hot spot (Fig. 4F). Based on the specific histopathological findings above, we ultimately confirmed the cause of subclinical CS as BMAH. There was no major complication, including UC exacerbation, during the perioperative period. On the 7th postoperative day, the urinary cortisol level decreased to 134 μg/day with 66% decrease of the baseline level, while the ACTH level slightly increased to 2.8 pg/mL. In contrast to the relatively stable status of dehydroepiandrosterone sulfate (240 ng/mL), testosterone was increased to 438 ng/dL, following the elevation of luteinizing hormone (7.10 mIU/mL) and follicle-stimulating hormone (8.84 mIU/mL). Hypertension was also improved but still persisted, which needed oral administration of azilsartan of 20 mg/day, spironolactone of 50 mg/day and nifedipine of 20 mg/day (Table 2). However, 1 month after the operation, the patient realized worsening abdominal symptoms, including bloody stool, abdominal pain and anorexia. A subsequent colonoscopy revealed abscesses, blood clots and continuous rough mucosa in the rectum, classified into moderate grade of the endoscopic severity. Therefore, the patient moved on to a remission induction therapy for UC exacerbation using systemic administration of prednisolone (40 mg/day). The dose of prednisolone was carefully reduced and azathioprine therapy was initiated.

Discussion

We reported a rare case of BMAH complicated with UC, in which we successfully obtained the improvement of hypercortisolemia based on the volume of the calculated adrenal glands by CT volumetry. The patient also maintained the endogenous cortisol level enough to avoid adrenal insufficiency. However, the concomitant UC was unexpectedly exacerbated after the surgery, which needed a remission induction therapy.

Three-dimensional CT volumetry is a reliable technique for the evaluation of organ or tumor size and commonly used for patients with lung cancer and living liver donors (Kamiya et al. 2018; Goja et al. 2018). Similarly, adrenal glands could be extracted in about 30 minutes, utilizing the difference in the attenuation value between adrenal glands and surrounding retroperitoneal adipose tissue (around −50 Hounsfield unit). In this case, based on the similar imaging findings among adrenal nodules, the resected adrenal volume was expected to correlate with the decrease in endogenous cortisol production after surgery. We, therefore, applied CT volumetry of adrenal glands to determination of operative strategy, resulting in successful management of his hypercortisolemia. There was a slight gap between the preoperatively estimated improvement in hypercortisolemia and its actual fall, which might result from postoperative elevation of ACTH and day-to-day variation of cortisol secretion. To examine the potential of CT volumetry for estimation of a surgical effect in BMAH, we retrospectively performed CT volumetry in 2 our historical cases with BMAH (Table 3). In the case 1, CT volumetry based on preoperative imaging calculated the resected right adrenal volume as 40.3% of the total adrenal volume, while the right adrenalectomy actually decreased urinary cortisol level by 45.9% of the preoperative level. In the case 2 where total right and partial left adrenalectomies were performed, CT volumetry on preoperative imaging estimated the resected adrenal volume as 85% of the total adrenal volume. After surgery, the urinary cortisol level decreased by only 46.0%, whereas the ACTH level increased from less than 2.0 to 10.3 pg/mL, indicating that improved ACTH secretion reduced the drop in the endogenous cortisol production. The major advantage of CT volumetry is that the measurement provides more detailed quantitative information on both adrenal gland volume than the other methods. As previously reported (Lamas et al. 2002), the findings of NP-59 scintigraphy and the diameters of adrenal tumors could not reflect the entire adrenal glands, resulting in the variety of postoperative improvement of the hypercortisolemia after adrenal surgery (Osswald et al. 2019). Taken together with the current case, our findings suggest that CT volumetry has a potential to predict the surgical effect on a hypothalamus-pituitary-adrenal axis.

As for surgical treatment in BMAH, bilateral total adrenalectomy had been an essential option for recalcitrant Cushing's syndrome (Reincke et al. 2015). Bilateral removal of adrenal glands needs lifelong replacement ther-

Table 3. Summary of baseline and postoperative status in our cases with bilateral macronodular adrenal hyperplasia.

	Age	Sex	Adrenal glands (mL, %)		Surgical procedure	Urinary cortisol (μg/day)		
			Right	Left		At diagnosis	After surgery	Decrease ratio (%)
The current case	53	Male	23 (24.7)	70 (75.3)	Left total adrenalectomy	396	134	66.1
Historical cases								
Case 1	72	Female	31 (40.3)	46 (59.7)	Right total adrenalectomy	357	193	45.9
Case 2	52	Male	85 (71.4)	34 (28.6)	Right total and left partial adrenalectomy	300	162	46.0

apy of glucocorticoids, but could completely abolish hypercortisolemia. However, the procedure also leads to increased surgical mortality compared with unilateral adrenalectomy, and one fifth of patients after bilateral adrenalectomy suffer from Nelson's syndrome or adrenal crisis (Reincke et al. 2015; Nagendra et al. 2019). In contrast, unilateral adrenalectomy has been reported to lead to remission in more than 90% of BMAH patients with a minimal risk for adrenal insufficiency (Vassiliadi and Tsagarakis 2019). Moreover, recently, a prospective cohort has reported the effectiveness of simultaneous removal of total and partial adrenal glands, so-called adrenal-sparing surgery, with no perioperative complications (Tanno et al. 2020). Therefore, both procedures are now expected as major surgical options for BMAH, although long-term follow-up for recurrence and additional treatment is required after surgery. CT volumetry could provide us sufficient quantitative information for those surgical options to appropriately control endogenous cortisol production in BMAH. However, the utility of CT volumetry remains to be investigated, particularly in BMAH cases harboring pathologically different lesions. Previous reports have shown that BMAH could be concomitant with aldosterone-producing adenomas, pheochromocytomas and also metastasis of non-adrenal origin (Tokumoto et al. 2017; Hayakawa et al. 2011; Vassiliadi and Tsagarakis 2019). Besides, BMAH is genetically heterogenous and the severity of hypercortisolemia could depend on the genetic causes (Espiard et al. 2015; Vassiliadi and Tsagarakis 2019). Therefore, the concomitant disorders and also the presence of germline mutation may influence the accuracy of the prediction based on CT volumetry.

For UC exacerbation in this case, it has been known that cortisol-lowering therapy with medical or surgical procedures could be a trigger for both new onset and exacerbation of autoimmune diseases such as rheumatoid arthritis and interstitial pneumonia in CS (Arima et al. 1998; Krysiak et al. 2013; Ohara et al. 2016). The postoperative exacerbation of UC in this case is also considered as one of episodes representing the immunological rebound after removal of hypercortisolemia (da Mota et al. 2011). Previous case series have reported that 16.7% of CS patients experienced immune dysfunction after remission of CS and the new onset and exacerbation were observed both in cases with and without need for postoperative glucocorticoid therapy (da Mota et al. 2011). Although the severity of hypercortisolemia has been reported to be associated with the incidence of immunological rebound, the association remains unclear. CT volumetry might be also helpful to examine the association between cortisol improvement and the risk for immune dysfunction after treatment for CS.

In conclusion, CT volumetry has a potential to assume the postoperative improvement of hypercortisolemia in BMAH, which may help the clinicians determine the operative procedure for BMAH and following medical treatment. However, clinicians should carefully follow the signs of immune-related disease in postoperative CS patients even if they maintain sufficient cortisol levels.

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Conflict of Interest

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