【 CASE REPORT 】

# Onset of Aortic Dissection Complicated with Cushing's Disease: A Case Report and Review of the Literature

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**Abstract:**
Cushing's syndrome and Cushing's disease cause various metabolic disorders associated with high cortisol levels. Some reports have shown that Cushing's syndrome is complicated with dissecting aortic aneurysm and aortic dissection after long-term exposure to high cortisol levels. We herein report a rare case of aortic dissection complicated with Cushing's disease. Aortic dissection may occur even under relatively short periods of high cortisol conditions. This case suggests that hypercortisolemia should be treated as soon as possible in order to prevent aortic dissection in subjects with Cushing's disease.

**Key words:** aortic dissection, Cushing's disease, diabetes mellitus, hypertension, dyslipidemia

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## Introduction

Cushing's syndrome and Cushing's disease cause metabolic disorders, such as diabetes mellitus (DM), hypertension and dyslipidemia, associated with hypercortisolemia, especially when the diagnosis of Cushing's syndrome or Cushing's disease is delayed and subjects are exposed to prolonged high cortisol levels. Following the first report by Lawrence et al., several reports have noted that Cushing's syndrome is complicated with dissecting aortic aneurysm or aortic dissection after long-term exposure to high cortisol levels (1). Among such cases, many are diagnosed with Cushing's syndrome simultaneously with the onset of aortic dissection (2-4). In addition, dissecting aortic aneurysm has been found incidentally when Cushing's syndrome was diagnosed (5-7), and a case of aortic dissection complicated with Cushing's disease, which resulted in death due to aortic dissection five years after removal of a pituitary adenoma, was also described (8).

We herein report a case of the onset of aortic dissection two months after the diagnosis of Cushing's disease. In addition, a review of the literature was conducted to further understand the onset of aortic dissection under continuous hypercortisolemia and its associated diseases.

## Case Report

A 75-year-old Japanese woman was referred to our office for poor glycemic control of DM. Her history included hypertension, dyslipidemia and DM, all diagnosed when she was 69 years old. She was taking 5 mg/day of amlodipine, 5 mg/day of lisinopril and 15 mg/day of urapidil for the treatment of hypertension; 10 mg/day of pravastatin for dyslipidemia; and 3 mg/day of glimepiride and 50 mg/day of sitagliptin for DM. She had no remarkable family history.

At that time, her height, body weight and body mass index (BMI) were 150.9 cm, 68.6 kg and 30.1 kg/m$^2$, respectively. Her vital signs on admission were as follows: temperature, 35.8°C; blood pressure, 124/68 mmHg; heart rate, 84 beats/min; oxygen saturation, 98% (room air). Table 1 shows her laboratory data on admission. Diabetes and dyslipidemia-associated data were as follows: plasma glucose, 153 mg/dL; plasma insulin, 7.4 μU/mL; hemoglobin A

**Table 1.   Laboratory Data on First Admission in This Subject.**

| Variable | Result | Reference range | Variable | Result | Reference range |
|---|---|---|---|---|---|
| Peripheral blood | | | Diabetes and dyslipidemia marker | | |
| White blood cells (/μL) | 9,680 | 3,300-8,600 | Plasma glucose (mg/dL) | 118 | |
| Neutrophil (%) | 80.0 | 28.0-78.0 | Hemoglobin A1c (%) | 9.2 | 4.9-6.0 |
| Red blood cells (×10⁴/μL) | 456 | 435-555 | Total cholesterol (mg/dL) | 255 | 142-248 |
| Hemoglobin (g/dL) | 14.8 | 13.7-16.8 | LDL cholesterol (mg/dL) | 167 | 65-139 |
| Hematocrit (%) | 44.1 | 35.1-44.4 | HDL cholesterol (mg/dL) | 66 | 40-90 |
| Platelets (×10⁴/μL) | 25.2 | 15.8-34.8 | Triglyceride (mg/dL) | 156 | 40-149 |
| Blood biochemistry | | | Endocrine marker | | |
| Total protein (g/dL) | 7.5 | 6.6-8.1 | ACTH (pg/mL) | 128.0 | 7.2-63.3 |
| Albumin (g/dL) | 4.3 | 4.1-5.1 | Cortisol (μg/dL) | 20.2 | 6.24-18.0 |
| Globulin (g/dL) | 3.2 | 2.2-3.4 | DHEA-S (μg/dL) | 190 | 76-386 |
| Total bilirubin (mg/dL) | 1.0 | 0.4-1.5 | TSH (μU/mL) | 1.173 | 0.35-4.94 |
| AST (U/L) | 23 | 13-30 | Free thyroxine (ng/dL) | 0.96 | 0.70-1.48 |
| ALT (U/L) | 29 | 10-42 | LH (mIU/mL) | 0.87 | 1.5-7 |
| LDH (U/L) | 300 | 124-222 | FSH (mIU/mL) | 32.67 | 3.5-10 |
| ALP (U/L) | 253 | 106-322 | Prolactin (ng/mL) | 17.8 | <15 |
| γ-GTP (U/L) | 39 | 13-64 | Growth hormone (ng/mL) | 5.07 | 0.13-9.88 |
| BUN (mg/dL) | 11 | 8-20 | IGF- I (ng/mL) | 147 | 52-163 |
| Creatinine (mg/dL) | 0.62 | 0.65-1.07 | Urinary test | | |
| Cholinesterase (U/L) | 261 | 240-486 | Urinary pH | 7.0 | 5.0-7.5 |
| Uric acid (mg/dL) | 4.1 | 2.6-5.5 | Urinary protein | ± | - |
| Creatine kinase (U/L) | 63 | 41-153 | Urinary sugar | 2+ | - |
| Amylase (μg/dL) | 109 | 42-118 | Urinary ketone body | - | - |
| CRP (mg/dL) | 0.06 | <0.14 | Urinary bilirubin | - | - |
| Sodium (mmol/L) | 141 | 138-145 | Urinary blood | - | - |
| Potassium (mmol/L) | 4.2 | 3.6-4.8 | Cortisol (μg/day) | 490 | 11.2-80.3 |
| Chloride (mmol/L) | 106 | 101-108 | | | |
| IP (mg/dL) | 2.7 | 2.7-4.6 | | | |
| Calcium (mg/dL) | 9.8 | 8.8-10.1 | | | |
| Magnesium (mg/dL) | 2.2 | 1.9-2.6 | | | |

AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyltranspeptidase, BUN: blood urea nitrogen, CRP: C-reactive protein, IP: inorganic phosphorus, LDL: low-density lipoproteins, HDL: high-density lipoprotein, ACTH: adrenocorticotropic hormone, DHEA-S: dehydroepiandrosterone sulfate, TSH: thyroid stimulating hormone, LH: luteinizing hormone, FSH: follicle stimulating hormone, IGF- I: insulin-like growth factor I

1c (HbA1c), 9.2%; glycoalbumin 23.2%; total cholesterol, 255 mg/dL; low-density lipoprotein (LDL)-cholesterol, 164 mg/dL; high-density lipoprotein (HDL)-cholesterol, 66 mg/dL; triglyceride, 156 mg/dL. Her liver and renal functions were near normal.

At this point, we evaluated the presence of macrovascular diseases in this patient. The maximum intima-media thickness was 0.7 mm, and no arterial stenosis was observed, although there was a 1.2-mm hyperintense plaque in the left-bifurcation. Echocardiography and abdominal ultrasound failed to detect any abnormalities, such as ischemic heart disease or aortic dissection. The ankle brachial pressure index (ABI) and pulse wave velocity (PWV) were as follows: right-ABI, 1.37; left-ABI, 1.21; right-PWV, 1,981; left-PWV, 2,096.

The co-existence of obesity, moon face and buffalo hump prompted an endocrinology examination. The data were as follows: adrenocorticotropic hormone (ACTH), 128.0 pg/mL; cortisol, 20.2 μg/dL; dehydroepiandrosterone sulfate
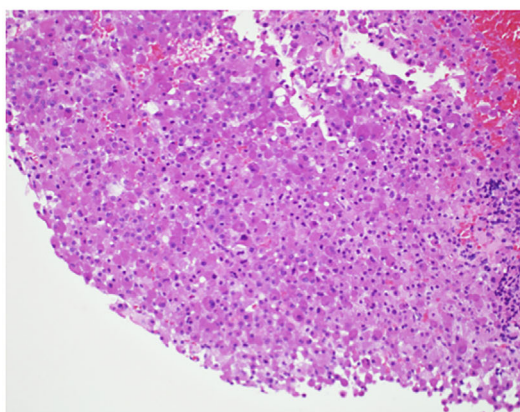
(DHEA-S), 190 μg/dL; prolactin, 17.8 ng/mL; luteinizing hormone, 0.87 mIU/mL; follicle stimulating hormone, 32.84 mIU/mL; growth hormone, 5.07 ng/mL; and insulin-like growth factor I, 147 ng/mL. Her urinary cortisol level was increased to 490 μg/day (reference range: 26.0-187.0 μg/day). The circadian rhythm of her serum cortisol revealed that her ACTH and cortisol levels were 85.3 pg/mL and 16.7 μg/dL at 22:00, respectively. Her cortisol level was not suppressed according to the 1 mg of dexamethasone suppression test (ACTH, 98.8 pg/mL; cortisol, 11.1 μg/dL) (high probability of Cushing's syndrome: cortisol, >5.0 μg/dL) and was partially suppressed according to the 8 mg of dexamethasone suppression test (ACTH, 95.8 pg/mL; cortisol, 6.7 μg/dL) (Cushing's disease: >50% reduction of plasma cortisol). The corticotropin-releasing hormone (CRH) test showed high levels of ACTH (103.3 pg/mL to 108.2 pg/mL) (Cushing's disease: >150% rise of ACTH) and cortisol (20.2 μg/dL to 31.1 μg/dL) continuously for 2 hours. A desmopressin challenge test was not performed, but enhanced

## Pituitary enhanced MRI
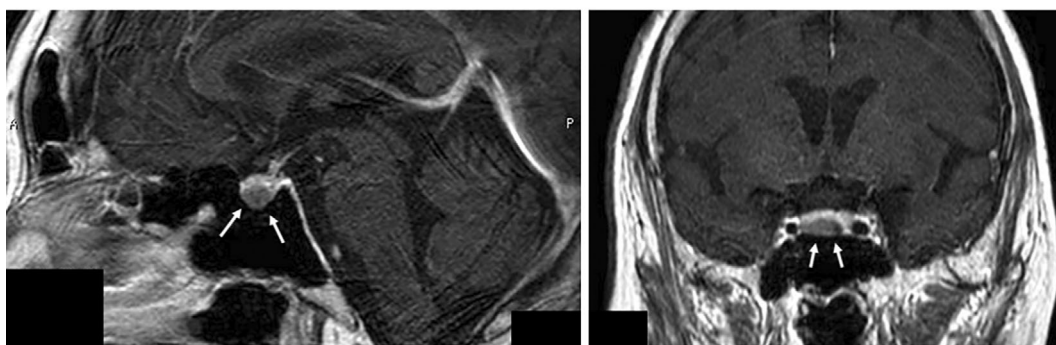
## Pituitary histopathological findings
### HE staining 10x20
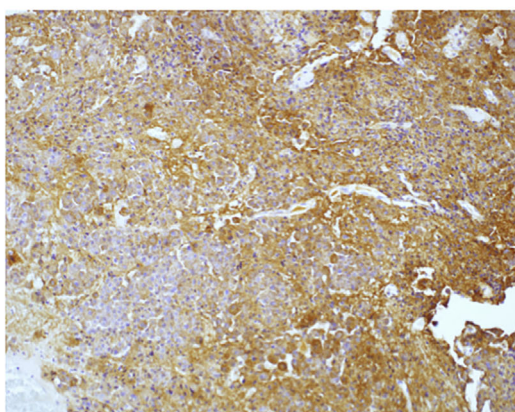### ACTH staining 10x10



**Figure 1.** **Pituitary enhanced magnetic resonance imaging (MRI) showed pituitary tumor (upper panel). The size of the pituitary tumor was up to 11 mm in diameter (white arrow). Histopathological findings (lower panel). Hematoxylin and Eosin staining of the pituitary gland (magnification10×20). The pituitary gland was filled with tumor cells with round nuclei and eosinophilic cytoplasm. ACTH staining of the pituitary gland (10×10). Pituitary adenoma cells were diffusely stained on ACTH staining.**

magnetic resonance imaging (MRI) revealed a pituitary tumor 11 mm in diameter (Fig. 1).

Since our patient had an 11-mm-diameter tumor in the pituitary area, we diagnosed her with Cushing's disease based on the clinical guidelines of the Japan Endocrine Society (https://doi.org/10.1507/endocrine.95.S.May_1), despite CRH test findings not meeting the criteria for Cushing's disease. It is possible that the presence of such a macro-tumor caused ACTH to interfere with the CRH test.

In addition, given the presence of the macro-tumor in the pituitary area, we did not perform bilateral simultaneous cavernous sampling. We discussed the need for a cortisol-lowering regimen for Cushing's disease with neuro- and vascular surgeon specialists but ultimately selected adenomectomy without a cortisol-lowing regimen because her cortisol levels were not high relative to her ACTH levels. We then scheduled adenomectomy after obtaining good glycemic control.

Just five days before adenomectomy and two months after the diagnosis of Cushing's disease, she experienced severe back pain and was brought to the emergency room. Two weeks earlier, her HbA1c level had been 8.0% with 4 U/day of insulin degludec, 0.9 mg/day of liraglutide and 500 mg/day of metformin, and her blood pressure had been 124/68 mmHg with 20 mg/day of nifedipine and 20 mg/day of azilsartan. Premonitory symptoms, such as infection, were not observed. Her emergency room vital signs were as follows: temperature, 34.8°C; blood pressure, 209/170 mmHg; heart rate, 100 beats/min; oxygen saturation, 94% (room air). As shown in Fig. 2 (right upper and right lower panel), chest and abdominal enhanced computed tomography (CT) revealed Stanford type A aortic dissection spreading from the aortic arch to the renal arterial branch that had not been observed three months earlier by chest or abdominal CT (Fig. 2 left panel). In addition, compared to abdominal CT performed three years earlier, a novel observation of mild
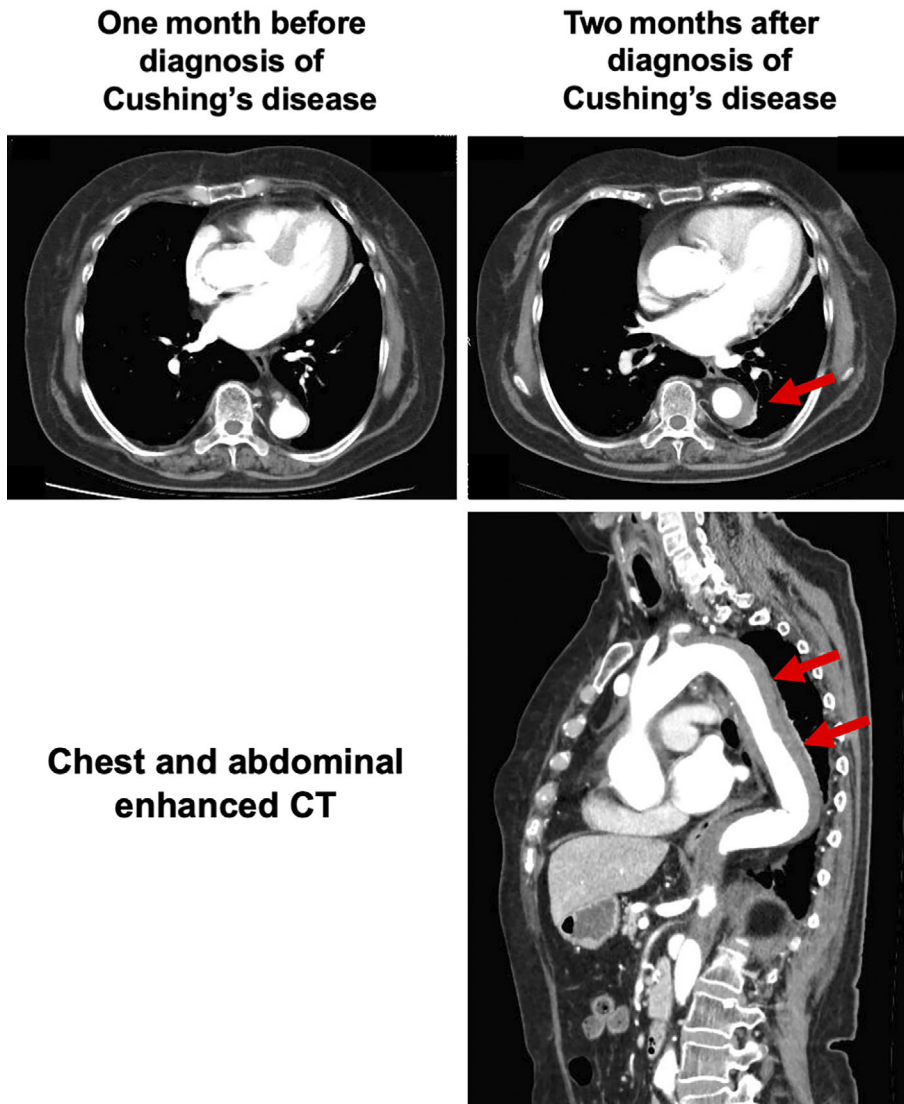
**One month before diagnosis of Cushing's disease**

**Two months after diagnosis of Cushing's disease**

**Chest and abdominal enhanced CT**



**Figure 2.** Chest and abdominal enhanced computed tomography (CT) one month before (left upper panel) and two months after (right upper and right lower panel) the diagnosis of Cushing's disease. Enhanced chest and abdominal CT two months after the diagnosis of Cushing's disease revealed Stanford type A aortic dissection spreading from the aortic arch to the renal arterial branch, although this had not been observed one month before the diagnosis.

calcification in the abdominal aorta was made on abdominal CT from three months earlier.

She was admitted to the intensive-care unit (ICU) for hypertension treatment and rest. We decided it would be better to perform adenomectomy as early as possible; her aortic dissection was caused by hypercortisolemia and its associated diseases. For safety, we performed adenomectomy three months after the onset of aortic dissection. We controlled blood pressure and blood glucose levels with hypotensive drug and insulin therapy. The pituitary adenoma was surgically removed by trans-nasal trans-sphenoidal endoscopy. Pituitary gland histopathology revealed tumor cells with round nuclei and eosinophilic cytoplasm. In addition, pituitary adenoma cells were diffusely stained by ACTH staining (Fig. 1). Her ACTH and cortisol levels were decreased to 5.2 pg/mL and 1.4 μg/dL, respectively, at 5 days post-operation.

She was finally discharged about one month after adenomectomy. She was prescribed 15 mg/day of hydrocortisone for the replenishment of adrenal hormone after pituitary adenomectomy, 20 mg/day of nifedipine and 1.25 mg/day of bisoprolol for the treatment of hypertension, 5 mg/day of rosuvastatin for dyslipidemia and 13 U/day of insulin aspart and 3 U/day of insulin degludec for DM.

## Discussion

We encountered a case of the onset of aortic dissection in a subject with Cushing's disease that was caused by hypercortisolemia and its associated metabolic diseases. We believe that the presence of hypercortisolemia due to Cushing's disease in addition to having various risk factors, such as DM, hypertension and dyslipidemia, finally led to the onset of aortic dissection in this subject.

**Table 2. A Summary of 9 Patients with Cushing's Syndrome or Cushing's Disease Complicated with Dissecting Aortic Aneurysm or Aortic Dissection.**

| Case | Reference | Gender | Age (years) | Diagnosis | Complication | Artery dissection | Timing of diagnosis |
|------|-----------|--------|-------------|-----------|--------------|-------------------|---------------------|
| 1 | 1 | M | 44 | Cushing's syndrome | - | Stanford B | After rupture of dissecting aneurysm |
| 2 | 2 | F | 45 | Cushing's syndrome | Hypertension | Right vertebral artery dissection | After the onset of aortic dissection |
| 3 | 3 | M | 30 | Cushing's syndrome | Hypertension, diabetes | Stanford B | At the same time with the onset of aortic dissection |
| 4 | 4 | F | 31 | Cushing's syndrome | - | Bilateral vertebral artery dissection | After the onset of aortic dissection |
| 5 | 5 | F | 55 | Cushing's syndrome | Hypertension, diabetes | Stanford B | At the same time with the onset of aortic dissection |
| 6 | 6 | M | 63 | Cushing's syndrome | Hypertension, diabetes | Stanford B | At the same time with the onset of aortic dissection |
| 7 | 7 | F | 38 | Ectopic ACTH syndrome | - | Cervical artery dissection | After the onset of aortic dissection |
| 8 | 8 | M | 26 | Cushing's disease | Hypertension | Stanford A | Rupture of dissecting aneurysm in autopsy 5 years after diagnosis of Cushing's disease |
| 9 | Ours | F | 75 | Cushing's disease | Hypertension, diabetes, Dyslipidemia | Stanford A | Aortic dissection only 2 months after diagnosis of Cushing's disease |

Chronic exposure to excess glucocorticoids results in a significant clinical burden in patients with Cushing's disease due to comorbidities, increased mortality and an impaired health-related quality of life. Recent studies have clearly demonstrated the effect of an early accurate diagnosis and treatment on the long-term outcomes (9-13). In everyday clinical practice, however, it is sometime difficult to diagnose and treat Cushing's disease at an early stage. Therefore, comprehensive endocrine management is often required in clinical practice.

Our patient had a macro-tumor in the pituitary gland, and the data were largely compatible with a Cushing's disease diagnosis, but the CRH test did not meet the criteria. It is possible that the presence of a macro-tumor resulted in interference with the ACTH reaction in the CRH test. It was reported that plasma ACTH levels were significantly increased following a CRH test in about 73% of cases pituitary macroadenomas with Cushing's disease but that almost all cases with such reactions were microadenomas (14, 15). Since our patient had a macro-tumor in the pituitary gland, we believe that this case falls into the remaining 27%.

Although Cushing syndrome is a known risk factor for dissecting aortic aneurysm, the association of Cushing syndrome with dissecting aortic aneurysm is extremely rare. Most reported cases of Cushing's syndromes complicated with dissecting aortic aneurysm and aortic dissection were adrenal Cushing's syndromes, not Cushing's disease. We performed a review of the literature and found only a few cases of aortic dissection (1, 3, 5, 6, 8) and vertebral or cervical artery dissection (2, 4, 7) published in this context. The comprehensive clinical data of nine cases from the literature are listed in Table 2.

Why there are so few reports of aortic dissection complicated with Cushing's disease remains unclear, although it is considered that Cushing's disease accounts for a large proportion of Cushing's syndrome cases (16). A reported positive correlation between the period of exposure to high serum cortisol levels and degree of hypertension suggests that long-term exposure to non-physiological hyper ACTH or cortisol levels leads to the onset of aortic dissection, rather than the degree of hyper ACTH and cortisol levels, for example (17). In addition, it is known that the mean age at the diagnosis of Cushing's disease is younger than that for Cushing's syndrome (10, 18-20). Furthermore, considering the increased number of subjects diagnosed with cortisol-secreting adrenal incidentalomas or subclinical Cushing's syndrome together with mild hypercortisolemia, it seems that patients with ACTH-independent Cushing syndrome suffer from hypercortisolemia for a relatively long period of time. Aortic dissection may thus be often complicated with Cushing's syndrome. Although how long our patient was exposed to high serum cortisol levels was unclear, aortic dissection was observed only two months after the diagnosis of Cushing's disease. As shown Fig. 2 (left panel), her dissecting aortic aneurysm or aortic dissection was not observed on chest or abdominal CT performed one month earlier. Since it takes longer to diagnose Cushing's disease than adrenal Cushing's syndrome, we should pay closer attention to signs and symptoms of pituitary Cushing's syndrome overlapping with common diseases (21).

Cardiovascular disorders are frequently complicated with hypertension, hyperglycemia, hypercholesterolemia, weight gain and prothrombotic state (22-24). Furthermore, Cushing's syndrome is associated with an increase in arterial

complications, including stroke (25). Hypercortisolemia-mediated cardiovascular complications, including myocardial infarction, congestive heart failure and stroke, account for high proportions of morbidity and mortality in untreated patients (26, 27). However, the association between arterial dissection and hypercortisolemia is less common, and it seems likely that hypercortisolemia causes arteriosclerosis, although its precise mechanism is unknown. There are some hypotheses concerning the mechanism underlying how hypercortisolemia leads to the onset and progression of arteriosclerosis. For example, high serum cortisol levels may affect the smooth muscle layer in the media of the aorta adjacent to cortisone-induced dissecting aneurysm, bringing about cellular metaplastic transformation of smooth muscle cells to fibroblast-like cells. In addition, high serum cortisol levels affect the vascular connective tissue (28, 29) and can increase the fragility of blood vessels, thus exerting negative effects by inhibiting collagen liposynthesis and increasing its catabolism (2).

Several limitations associated with the present study warrant mention. First, although we think that the presence of Cushing's disease was, at least in part, associated with the onset of aortic dissection in this case, we cannot exclude the possibility that her aortic dissection was induced incidentally, regardless of the presence of Cushing's disease. Second, since she suffered from hypertension, dyslipidemia and DM for over six years, it cannot be denied that such comorbidities were major factors associated with the arterial dissection. Third, it may have been better to consider other treatments for hypercortisolemia. As shown in case presentation section, we selected adenomectomy without a cortisol-lowering regimen. We assumed that if we had been treated her with a cortisol-lowering regimen, the aortic dissection might have been prevented. Surgical resection of the underlying tumor is the standard care for patients with Cushing's syndrome. Medical therapy mainly serves as an option for patients who are not suitable for surgery or have recurrent disease. In Japan, mitotane, trilostane and metyrapone have been approved for the treatment of endogenous Cushing's syndrome, and long-acting pasireotide has been approved for the treatment of Cushing's disease.

The primary goal of medical therapy in Cushing's disease is to reduce high serum cortisol levels (30). For these reasons, we discussed a possible therapy plan with neurosurgeons, prioritizing surgical treatment. In addition, the patient's cortisol level was not extremely high compared to the ACTH level, and other complications, such as hypertension, dyslipidemia and DM, were able to be managed with medication. Given the above findings, we should bear in mind that hypercortisolemia with Cushing's disease in addition to Cushing's syndrome can cause aortic dissection. In addition, although the combination of Cushing's disease and aortic dissection is rare compared to Cushing's syndrome, such combination is not completely unforeseeable. Therefore, it is better to improve high cortisol levels as soon as possible in order to prevent aortic dissection in subjects with Cushing's syndrome and Cushing's disease.

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