Cyclic Cushing’s syndrome caused by neuroendocrine tumor: a case report

Kewei Wang1) *, Fuqiang Liu2),3),4) *, Chuanlong Wu3),4), Yan Liu3),4), Lin Qi3),4), Xiaohan Yang3),4), Huizhen Zheng2), Aixia Ma2), Jiahui Wu3), Fei Yan3),3),4), Xinguo Hou2),3),4), Li Chen2),3),4), Ming Dong2),3),4) and Weikai Hou2),3),4)

1) School of Medicine, Shandong University, Jinan 250012, China
2) Department of Endocrinology, Qilu Hospital of Shandong University, Jinan 250012, China
3) Institute of Endocrine and Metabolic Diseases of Shandong University, Jinan 250012, China
4) Key Laboratory of Endocrine and Metabolic Diseases, Shandong Province medicine & health, Jinan 250012, China

Abstract. Cushing’s syndrome (CS) is a clinical syndrome characterized by hypercortisolism. Cyclic Cushing’s syndrome (CCS), which exhibits a periodic or irregular increasing pattern in cortisol, is a rare type of Cushing’s syndrome. A 37-year-old man came to our hospital because of repeated dizzy spells, weakness and hypercortisolism lasting two weeks. Endocrinological examinations indicated CCS with periodic and intermittent increases in cortisol. Enhanced computed tomography (CT) revealed space occupying lesions on the upper lobe of left lung, and biopsy eventually proved that these were pulmonary carcinoid tumors with ectopic ACTH secretion, which was subsequently manifested a Cushing’s syndrome. PET-CT, ultrasound and biopsy of the thyroid gland indicated bilateral thyroid papillary carcinoma. CT scan showed bilateral nodular hyperplasia of the adrenal gland. Enhanced magnetic resonance imaging (MRI) confirmed that the high signal disappeared on the posterior lobe of the pituitary gland and that the pituitary stalk shifted left, which was suspected to be non-functional pituitary microadenoma. The patient underwent surgery involving resection of the left upper pulmonary lobe and the mediastinal lymph node around the hilus pulmonis, which resulted in complete remission of CCS. The patient then chose elective surgery for the thyroid papillary carcinoma. An analysis of the patient’s genomic DNA identified a novel mutation in PDE11A: c.2032 (exon 12) G > A, which is associated with primary pigmented nodular adrenocortical disease (PPNAD). This is a novel mutation which has been no previous public clinical report on this mutation as it relates to this disease.

Key words: Cyclic Cushing’s syndrome, Neuroendocrine tumor, Primary pigmented nodular adrenocortical disease (PPNAD), PDE11A

CUSHING SYNDROME (CS) results from hypercortisolism caused by pituitary adenoma, ectopic ACTH tumors, adrenocortical carcinoma or hyperplasia. However, cyclic Cushing’s syndrome (CCS) refers to cyclic and periodic production of cortisol [1]. Until now, relevant clinical reports of CCS have remained limited.

Patients with CCS exhibit substantial fluctuations in cortisol levels over time, so that clinical features may be quite varied and complex, rendering diagnosis of this disease is quite difficult.

The possibility of CCS should be considered in patients who appear to go through periods of spontaneous recurrence and remission of hypercortisolism. Low-dose (0.50 mg) and high-dose (2 mg) dexamethasone suppression tests (DST) can be used to identify the type of Cushing’s syndrome.

Treatment consists, whenever possible, of surgical excision of the tumor after controlling the hypercortisolism. Medical intervention is the treatment of choice to produce a rapid decrease in high glucocorticoid levels.

Case Report

A 37-year-old man was admitted to our hospital on June 15, 2016 because of repeated attacks of dizziness, weakness and hypercortisolism lasting two weeks. A year prior, he felt dizzy and weak and experienced facial edema without any obvious cause. He was admitted to a local hospital with a diagnosis of “interstitial lung dis-
ease” 6 months ago. His blood pressure was 154/94 mmHg; the lowest serum potassium was 2.43 mmol/L. After shock therapy with methylprednisolone, anti-inflammatory and potassium supplement treatment lasted 8 days. The pneumonia syndrome was well controlled. Three months ago, the patient experienced limb edema and took spironolactone without a doctor’s recommendation. The curative effect was not good but the symptoms later underwent remission. One month earlier, he was admitted to a local hospital for central obesity. One round of endocrinologic examinations of serum cortisol and 24-h UFC demonstrated first increasing levels and a second round normal level (Table 1). He was then hospitalized again after his highest blood pressure reaching 180/110 mmHg. Since the onset of disease, he had gained 5 kg in body weight.

The patient was referred to our hospital for further evaluation and treatment. Upon admission, he presented with Cushingoid features (moon face, central obesity, purpura and body mass index of 27.5 kg/m²) (Fig. 1),

Table 1  Measurement on serum cortisol, serum ACTH and 24 hUFC of the patient

| Time            | Serum cortisol (μg/dL) | Serum ACTH (pg/dL) | 24 hUFC (nmol/24 h) |
|-----------------|------------------------|--------------------|---------------------|
| 2016.03.06      | 39.10                  | Not measured       | 575.8               |
| 2016.05.19      | 6.23                   | Not measured       | 88.7                |
| 2016.06.05      | >63.31                 | Not measured       | 10,827.2            |
| 2016.06.16  8:00 | 4.39                   | 58.18              | 105.0               |
|                | 16:00 5.84             |                    |                     |
|                | 0:00 5.34              |                    |                     |
| 2016.07.02  8:00 | 128.80                 | >1,500.00          |                     |
|                | 16:00 55.74            | 177.90             | >14,193.8           |
|                | 0:00 60.00             | 207.70             |                     |
| 2016.07.20  8:00 | 10.61                  | 15.73              | 103.6               |
| 2016.08.19  3:00 | 3.71                   | 17.68              | 65.8                |

ACTH, Adrenocorticotropic hormone; 24-h UFC, 24-hours urinary free cortisol; Normal reference range: serum cortisol 8:00 8.7–22.4 μg/dL, 16:00 <10 μg/dL; serum ACTH, 4.7–48.8 pg/dL; 24-h UFC, 9.6–124.0 nmol/24 h.

Fig. 1  Clinical features of Cushing’s syndrome.

The patient presented with central obesity (A), moon face (B), and purpura on his legs (C).
hypertension, and hypokalemia (Table 2) although he had consistently taken potassium supplementation. Insistent examinations of the level of cortisol demonstrated losing regular ultradian rhythm, which was not consistent with the clinical symptoms of hypercortisolemia (Table 1). PTH level was higher than normal limits and bone density film showed osteoporosis and a high risk of fracture. A 75-g oral glucose tolerance test (OGTT) confirmed impaired glucose tolerance (IGT) (0-min: 4.72 mmol/L and 120-min: 8.26 mmol/L), and the function of islet cells was normal. The wide use of plasma aldosterone/plasma rennin activity ratio (ARR) as a marked increase in the detection rate of primary aldosteronism (Table 3) [2]. The ratio less than 3.7, which can rule out primary aldosteronism [3]. Endocrinological examination of 17α-OHP, androstenedione and dehydroepiandrosterone sulfate (DHEAS) levels were normal, which ruled out congenital adrenal cortical hyperplasia (CAH) and indicated the possibility of endogenous Cushing’s syndrome [4]. Functional endocrine tests revealed a lack of ACTH/cortisol circadian rhythms and no suppression in response to an overnight low-dose (0.50 mg) and high-dose (2 mg) dexamethasone suppression test (DST) (Tables 4, 5), which suggested ectopic ACTH. Combinations of repeated examinations of serum cortisol and 24-h UFC, the level of serum cortisol showed a cyclic pattern as it peaked three times and bottomed out twice (Table 1). These examinations confirmed the diagnosis of CCS and that its fluctuation cycle was 30 days.

Enhanced CT of the lung revealed space occupying lesions on the upper lobe of the left lung (Fig. 2). Combined with a pulmonary pathological biopsy, the diagnosis was pulmonary carcinoid tumor, a kind of pulmonary neuroendocrine tumor. CT scan of the adrenal gland indicated bilateral adrenal nodular hyperplasia and hyper trophy (Fig. 3). PET-CT, ultrasound and biopsy of the thyroid gland indicated bilateral thyroid papillary carcinoma. Enhanced magnetic resonance imaging (MRI) showed that the high signal disappeared on the posterior lobe of the pituitary gland, and the pituitary stalk shifted

### Table 2 Clinical and biochemical data of the patient after hospitalization

|                        | After Hospitalization | Normal Range       |
|------------------------|----------------------|--------------------|
| SBP/DBP (mmHg)         | 131/90               | 90–120/60–80       |
| BMI                    | 27.5                 | 18.5–23.9          |
| Potassium (mmol/L)     | 2.96                 | 3.5–5.5            |
| TG (mmol/L)            | 13.79                | 0.30–1.70          |
| Glutamate dehydrogenase (GLDH) (U/L) | 35.4               | <7.4               |
| Alkaline phosphatase (AKP) (U/L) | 134                 | 45–125             |
| Progastrin-releasing peptide Pro-GRP (ng/L) | 91.26            | <50                |
| LH (mIU/mL)            | 0.98                 | 1.5–9.3            |
| FSH (mIU/mL)           | 0.43                 | 1.5–12.4           |
| Prolactin (PRL) (ng/mL)| 26.13                | 2.1–17.7           |
| TSH (uIU/mL)           | 2.61                 | 0.35–5.5           |
| PTH (pg/mL)            | 76.98                | 15–65              |

### Table 3 Plasma aldosterone/plasma rennin activity ratio (ARR)

|                        | Renin (uIU/mL) | Aldosterone (ng/dL) | Aldosterone/rennin activity ratio (ARR) |
|------------------------|---------------|---------------------|----------------------------------------|
| Clinostatism           | 5.70          | 5.62                | 0.98                                   |
| Orthostatism           | 14.00         | 7.84                | 0.56                                   |

### Table 4 Low-dose (0.50 mg) dexamethasone suppression test (DST)

| Day | Cortisol (ug/dL) at 8:00 |
|-----|-------------------------|
| 1   | 128.8                   |
| 2   | 90.25                   |

### Table 5 High-dose (2 mg) dexamethasone suppression test (DST)

| Day | Cortisol (ug/dL) at 8:00 |
|-----|-------------------------|
| 1   | 128.8                   |
| 2   | 119                     |
left (Fig. 4). Endocrinological hormonal data showed PRL level was higher than normal range but less than 200 ng/mL, while LH and FSH level was less than normal limits (Table 2). MRI and hormonal data both suggested non-functional pituitary microadenoma [5].

Therapy: The patient underwent a left lung upper lobe resection and pulmonary portal mediastinal lymph node dissection by single port laparoscopic surgery. The dissection area of the tumor was 1.8 cm × 1.6 cm. The pathology demonstrated neuroendocrine tumors (Fig. 5). Immunohistochemical examinations showed ACTH(+), CK(+), CK7 cell(+), Syn(+), CgA(+), CD56(+), TTF-1(+), CK5/6(–) and P63(–). After the operation, reexamination of serum and urinary cortisol showed normal values (Table 1). Then the patient chose an elective surgery for his thyroid papillary carcinoma.

**Discussion**

Cyclic Cushing’s syndrome (CCS) refers to the excess production of cortisol with a cyclic or periodic pattern. Patients with CCS do not have unique, fixed clinical features. Spontaneous periodic and irregularly occurring fluctuations in common manifestations of Cushing’s
syndrome, including excess weight, central adiposity, edema, hypertension, hypokalemia or hyperglycemia, during the course of the illness have been noted.

At present, reported cases of CCS are quite rare. It is difficult to identify the fluctuating symptoms of the disease so that the diagnosis is not easy. Thus, regular detection of serum cortisol and the results of dexamethasone suppression testing should be viewed with extreme caution in patients who was suspected with CCS. The diagnosis of cyclicity has been defined as the occurrence of at least three peaks and two troughs of plasma cortisol level [6].

In this patient, levels of Pro-GRP was high before the operation but it decreased to normal after the operation, which proved that increased Pro-GRP is a marker for neuroendocrine lesions. Although Pro-GRP is used as a serum tumor marker for small cell lung cancer (SCLC), elevated serum Pro-GRP concentrations have been observed in some non-small-cell lung cancers (NSCLCs). Serum Pro-GRP-positive patients may have manifested neuroendocrine differentiation, which can be used to predict the locations of lesions and prognosis of the disease [7]. After the pulmonary carcinoid operation, the CCS was released.

The precise mechanism of periodic hypercortisolism is largely unknown. Cyclic Cushing’s syndrome can be caused by adrenal hyperplasia or tumor, hypophysoma and ectopic ACTH tumor. Influences of ghrelin as well as changes in dopaminergic tone have been described as possible underlying mechanisms [8]. Tumor infarction and periodic spontaneous bleeding would be an alternative explanation for periodic ACTH and cortisol release [9]. Cyclic Cushing’s syndrome should be suspected in a patient with typical clinical findings of Cushing’s syndrome but normal biochemistry. Repeated measurement of serum ACTH and urinary cortisol excretion is required to establish the diagnosis.

To explore the genetic reason of cyclic Cushing’s syndrome, we conducted a whole-genome association study of this patient and found a single base-pair mutation: c.2032 (exon 12) G > A in PDE11A (rs201629965) on chromosome 2. A whole-genome association study found a single base-pair mutation: c.2032 (exon 12) G > A in PDE11A (rs201629965) on chromosome 2. The genetic defect was a missense mutation in the PDE11A gene, which was linked to primary pigmented nodular adrenocortical disease (PPNAD) type 2, a rare form of ACTH-independent Cushing’s syndrome.

The patient was presented with cushingoid features (moon face, central obesity, purpura and body mass index of 27.5 kg/m²) accompanied with hypertension (131/90 mmHg) and hypokalemia. These symptoms accord with clinical manifestation of PPNAD [10]. Based on the novel mutation and symptoms of the patient, PPNAD may exist in the patient. However, adre-
nal biopsy and pathological examination which may confirm the existence of PPNAD in this patient were not performed, since the reexamination of endocrinological data showed normal values and symptoms of the patient turned to be better after the operation. In addition, the patient’s parents have been dead for many years, and he doesn’t have any siblings, so we couldn’t learn whether his diseases were hereditary and perform genetic analysis in his immediate family. Therefore, whether PPNAD exists in this patient contributing to the occurrence of CCS needs further exploration.

In this case, the patient was diagnosed with pulmonary neuroendocrine tumors, bilateral thyroid papillary carcinoma, and suspected to have non-functional pituitary microadenoma and PPNAD. The genetic mutation c.2032 (exon 12) G > A in PDE11A (rs201629965) provided opportunities for further exploration in pathogenesis of PPNAD. To explore pathogenicity of the genetic mutation, we will still plan for a follow-up visit to this patient.

Acknowledgements
This work was financially supported by Shandong Provincial Natural Science Foundation, China (grant number ZR2016HB34).

Disclosure
None of the authors have any conflicts of interest associated with this research.

Reference
1. Velez DA, Mayberg MR, Ludlam WH (2007) Cyclic cushing syndrome: definitions and treatment implications. Neurosurg Focus 23: E4, discussion E4a.
2. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, et al. (2016) The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 101: 1889–1916.
3. Mulatero P, Stowasser M, Loh KC, Fardella CE, Gordon RD, et al. (2004) Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. J Clin Endocr Metab 89: 1045–1050.
4. Merke DP, Bornstein SR (2005) Congenital adrenal hyperplasia. Lancet 365: 2125-2136.
5. Molitch ME (2012) Management of incidentally found nonfunctional pituitary tumors. Neurosurg Clin N Am 23: 543–553.
6. Meinardi JR, Wolffentutel BH, Dullaart RP (2007) Cyclic Cushing’s syndrome: a clinical challenge. Eur J Endocrinol 157: 245–254.
7. Kudo K, Ohyanagi F, Horiike A, Miyauchi E, Yanagitani N, et al. (2011) Clinicopathological findings of non-small-cell lung cancer with high serum progastrin-releasing peptide concentrations. Lung Cancer 74: 401–404.
8. Arnaldi G, Mancini T, Kola B, Appolloni G, Freddi S, et al. (2003) Cyclical Cushing’s syndrome in a patient with a bronchial neuroendocrine tumor (typical carcinoid) expressing ghrelin and growth hormone secretagogue receptors. J Clin Endocrinol Metab 88: 5834–5840.
9. Meinardi JR, Van den Berg, Wolffentutel BH, Kema IP, Dullaart RP (2006) Cyclical Cushing’s syndrome due to an atypical thymic carcinoid. Neth J Med 64: 23–27.
10. Stratakis CA, Kirschner LS (1998) Clinical and genetic analysis of primary bilateral adrenal diseases (micro- and macronodular disease) leading to Cushing syndrome. Horm Metab Res 30: 456–463.