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CASE REPORT

A Case of Cushing Disease Masked by Symptoms of Bipolar Disorder

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Abstract

BACKGROUND: Cushing disease is a rare but serious endocrine disorder. It involves increased cortisol levels, which can damage the function of various systems throughout the body, including the central nervous system, affecting cognition, memory, and emotion. However, it is rare that Cushing disease presents as a mental disorder. This paper reports the complete diagnosis, treatment process, and follow-up of a patient with Cushing disease whose main symptom was bipolar disorder.

CASE PRESENTATION: A 31-year-old woman was diagnosed with bipolar disorder 9 years ago and was admitted to hospital several times due to repeated episodes of depression and mania. In October 2017, after careful examination and consideration by doctors, the patient was diagnosed with Cushing syndrome and underwent transsphenoidal pituitary microadenoma resection. Glucocorticoid replacement therapy and antipsychotic therapy were administered postoperatively. After careful treatment and care by the medical staff, the patient's cortisol levels returned to normal, and her mental symptoms were significantly improved.

CONCLUSION: This is a rare case of Cushing disease marked by psychiatric symptoms. Neuropsychiatric symptoms can precede the onset of Cushing disease, making diagnosis challenging.

INTRODUCTION

Cushing syndrome (CS), also known as hypercortisolism, is a rare but serious disease. It is a chronic and systemic endocrine disease with complex etiology and diverse symptoms and signs. Typical manifestations include central obesity, purple skin marks, hypertension, abnormal glucose metabolism, and hypokalemia. The annual incidence of CS is about 40 cases per million people, with a ratio of about one to three men to women (Pivonello *et al.* 2016; Pivonello 2015a; Steffensen *et al.* 2010). 70% of CS is caused by adrenocorticotropic hormone (ACTH) hypersecretion, which is

a condition called Cushing disease (CD) (Pivonello *et al.* 2016; Pivonello 2015a; Steffensen *et al.* 2010).

In CD, a tumor autonomously secretes ACTH, leading to excess cortisol secretion from the adrenal glands and, consequently, a disordered circadian rhythm regarding cortisol. Patients with long-term excessive plasma cortisol levels exhibit various clinical problems and increased mortality (van Haalen *et al.* 2015; Ntali *et al.* 2013). The abundance of glucocorticoid receptors in the central nervous system makes it susceptible to excessive levels of glucocorticoids (such as cortisol), causing cognitive, memory, and emotional abnormalities (Pivonello *et al.* 2016; Chen *et al.* 2013; Feelders *et al.* 2012. Depression is the most commonly described psychiatric co-morbidity in CS (Sonino *et al.* 2010). A study by Sonino *et al.* (1998) found that, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria, 54% of patients with CD had major depressive disorder. Another three studies, involving 711 patients with CD across multiple countries, found that 260 patients (36.6%) experienced depression or some other form of psychiatric disturbance (Pecori *et al.* 2003; Storr *et al.* 2011; Valassi *et al.* 2011).

When a CD patient is first diagnosed with an acute mental disorder, it is easy to fail to consider the primary disease, resulting in misdiagnosis and mistreatment. Herein, we report on a case of CD that was misdiagnosed and treated as bipolar disorder for 9 years. After proper identification and treatment of CD, the patient exhibited improvement in the functional disorder, which continued with maintenance treatment.

CASE PRESENTATION

The patient, a 31-year-old female, was admitted to the Psychiatric Department of the Third Affiliated Hospital of Sun Yat-Sen University on October 6, 2017, with severe manic symptoms and was confined to bed. The patient claimed that she was God and thought she was powerful. She was hospitalized due to her depressed mood and suicidal ideation. On October 25, 2017, she was transferred to the Endocrine Department due to the fact that she exhibited abnormal blood glucose fluctuations. She had previously been diagnosed with bipolar disorder and diabetes.

Since the onset of the affective disorder in 2009, the patient had been hospitalized many times for mood changes, and had been diagnosed with bipolar disorder. She was treated with various psychotropic drugs and underwent modified electroconvulsive therapy (MECT), but her symptoms repeatedly reoccurred over the years.

The patient's heart rate was 138 beats/min, blood pressure was 152/110 mmHg, and random blood glucose was 12.6 mmol/L when she was hospitalized on October 6, 2017. She had a full moon face, rosy complexion, scattered acne on the face, violaceous striae on the abdomen, and scattered purpura on the limbs. Additionally, she had central obesity, dorsocervical fat pads, abdominal panniculus, and multiple skin wounds on both lower limbs, with fluid exudation and edema. Psychiatric examination showed that she had clear consciousness and was well oriented to time and place, but she was uncooperative during the examination. She was not at ease in hospital and so was confined to her hospital bed. She had a high voice, rapid speech, and spoke a great deal, as well as shouting. She denied having hallucinations and delusion of grandeur. She also exhibited emotional excitement, irritation, and physical hyperactivity, with partial self-knowledge.

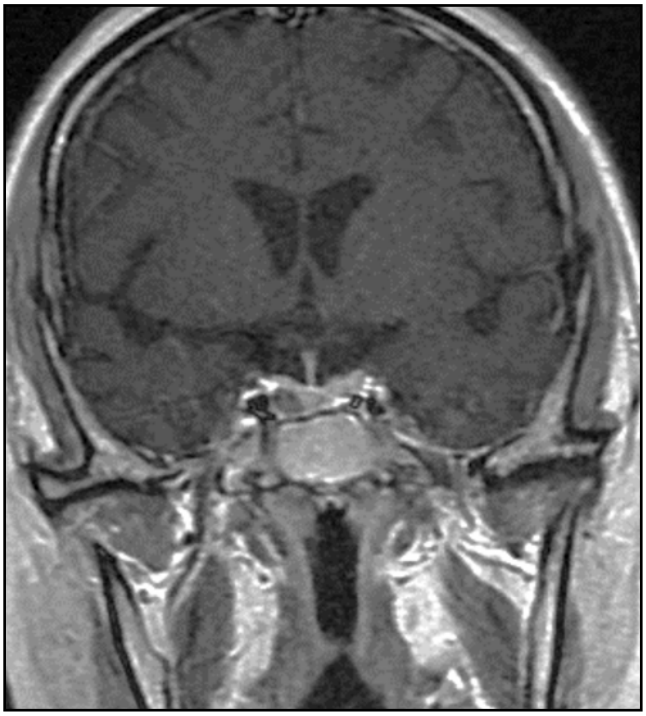

Fig. 1. MRI showing a pituitary microadenoma

In September 2017, the patient underwent an adrenal function examination. Regarding plasma cortisol, she had levels of 1420, 922.3, and 838.7 nmol/L at 08:00, 16:00, and 24:00, respectively. Regarding ACTH, she had levels of 22.94, 19.5, and 14.72 pmol/L at 08:00, 16:00, and 24:00, respectively. A dynamic contrast-enhanced MRI scan revealed a microadenoma (about 7×4 mm in size) on the right side of the pituitary gland (Figure 1). Plain and enhanced abdominal computed tomography (CT) scans indicated bilateral adrenal gland thickening (adrenal hyperplasia was considered) and significantly decreased liver density (severe fatty liver was considered). Furthermore, a chest CT scan with contrast indicated a high possibility of pneumonia and an abscess in the right upper lung. Laboratory analysis indicated infection, anemia, hypokalemia, and hyperuricemia (Tables 1 and 2). The patient was treated with insulin, antipsychotic therapy (quetiapine fumarate, 0.1 g qd + 0.2 g qn; clozapine, 25 mg qd + 50 mg qn; lamotrigine, 25 mg qd), anti-infection medication (sulbactam, 3

Tab. 1. Routine blood tests

Item	10/06/2017	11/7	11/11	11/15	Normal range
WBC (10^9/L)	10.13↑	6.38	9.24	11.72↑	3.5–9.5
ANC (10^9/L)	8.86↑	5.07	7.83↑	10.4↑	1.8–6.3
RBC (10^{12}/L)	3.39↓	2.99↓	3.16↓	3.13↓	3.8-5.1
HGB (g/L)	106↓	94↓	100↓	98↓	115–150

WBC: white blood cell; ANC: absolute neutrophil count; RBC: red blood cell; HGB: hemoglobin

Tab. 2. Biochemical indexes

Item	10/06/2017	10/26	11/06	11/07	11/11	Normal range
ALT (U/L)	141↑	46↑	38	35	22	3–35
AST (U/L)	52↑	23	18	18	16	13–35
K (mmol/L)	1.93↓	3.27↓	4.03	2.81↓	3.53	3.5–5.3
Na (mmol/L)	148	143	145	143	145	137–147
PCT (mg/ml)	/	1.34↑	/	/	0.25	<0.5
HbA1c (%)	9.5↑					<7%
LH (mIU/ml)	/	0.07↓	/	/	/	15.9–54
FSH (mIU/ml)	/	0.47↓	/	/	/	23–116.3
24-h UK (mmol/24h)	/	152.4↑	/	/	/	25–100

ALT: alanine transaminase; AST: aspartate aminotransferase; K: potassium; Na: sodium; PCT: procalcitonin; HbA1c: glycated hemoglobin; LH: luteinizing hormone; FSH: follicle-stimulating hormone; 24-h UK: 24-hour urine potassium

g bid; voriconazole, 0.2 g bid iv drip), and potassium supplementation.

On October 29, 2017, the patient had a high 24-h urinary free cortisol (UFC) level of 3419 nmol/24h. By October 31, 2017, the 24-h UFC had decreased to 2146.250 nmol/24h. Table 3 shows the changes in the serum cortisol and ACTH circadian rhythm from September 12, 2017 to June 18, 2019 (treatment for CD was started on November 20, 2017). The psychiatric assessment on October 6, 2017 indicated that the patient had a severe mental disorder, with Young Mania Rating Scale (YMRS) and 17-item Hamilton Depression Rating Scale (HAMD-17) scores of 24 and 34, respectively. Based on the above physical and laboratory examination results, we determined that the patient conformed to the clinical features of CD.

The patient underwent bilateral inferior petrosal sinus (IPS) sampling on November 2, 2017. The ACTH levels on the left side of the inferior petrosal sinus were 27.1, 22.6, and 25.8 pmol/L. The ACTH levels on the right side of the inferior petrosal sinus were 124.9, 156.1, and 117.8 pmol/L. The ACTH levels in the peripheral venous blood (PVB) were 23.1 and 24.6 pmol/L. The left side IPS/PVB ratio was about 1.17, and the right side IPS/PVB ratio was about 6.35. After multidisciplinary consultations involving the Endocrinology, Neurosurgery, and Psychiatry Departments at the hospital, the patient's diagnosis was updated to CD with mood disorder on November 4, 2017.

On November 20, 2017, the patient underwent resection of the pituitary microadenoma. After the operation, the patient was given glucocorticoid replacement therapy involving hydrocortisone (cortisol, 50 mg q8h), anti-infection treatment (piperacillin-tazobactam, 4.5 g q8h; voriconazole, 0.2 g bid), an antiarrhythmic (propranolol, 10 mg tid), and oral drugs to control her mood such as quetiapine fumarate (0.2g q12h) and lamotrigine (50 mg bid).

On November 22, 2017, the patient underwent an adrenal function examination. Regarding plasma cortisol, she had levels of 1239.29, 965.24, and 401.09 nmol/L at 08:00, 16:00, and 24:00, respectively. Regarding ACTH, she had levels of 9.44, 7.73, and 2.99 pmol/L at 08:00, 16:00, and 24:00, respectively. Chest CT reexamination showed that the inflammation in both lungs was significantly improved and the abscess in the right upper lung was smaller than before. The pathology results revealed a pituitary microadenoma, and the immunohistochemistry analyses indicated positive ACTH and prolactin (PRL) results. The operation was successful and there were no complications. On December 5, 2017, the patient was discharged in a stable mental condition, with YMRS and HAMD-17 scores of 5 and 8, respectively.

On March 1, 2018, the patient returned to the hospital for a second visit. The 24-h UFC results were 185.66, 148.24, and 108.96 nmol/24h (within the normal range). The plasma ACTH and cortisol circadian rhythm results are shown in Table 3. Her

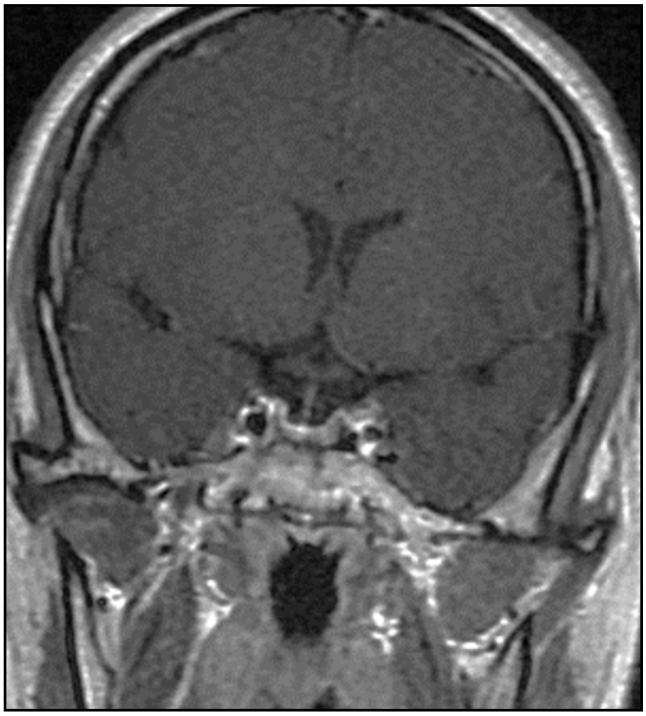

Fig. 2. MRI showing complete removal of pituitary microadenoma

psychotic symptoms had not recurred. The glucocorticoid replacement therapy (cortisol, 10 mg qd) and antipsychotic therapy (quetiapine fumarate, 0.1 g qd+0.2 g qn; clozapine, 25 mg qd + 50 mg qn; and lamotrigine, 25 mg qd) were continued.

On June 18, 2019, the patient returned for a routine follow-up. Her 24-hour UFC results were 328.560 and 313.85 nmol/24h (within the normal range). The plasma ACTH and cortisol circadian rhythm results are shown in Table 3. The MRI showed that the pituitary microadenoma was completely removed (Figure 2). The YMRS and HAMD-17 scores were 7 and 14, respectively. The glucocorticoid replacement therapy was gradually stopped. The Psychiatric Department adjusted her medication regimen, which involved quetiapine fumarate (0.2 g qn) and clozapine (25 mg qd + 50 mg qn), and she also started taking sertraline hydrochloride (50 mg qd). She was instructed to return for regular follow-ups at the Psychiatric and Endocrinology Departments and to follow the medication regime after discharge.

DISCUSSION

This case involved a Chinese woman with symptoms consistent with bipolar disorder, who was therefore diagnosed with bipolar disorder by doctors a long time ago based on her symptoms. CD has repeatedly been associated with psychopathology in the scientific literature, with major depression disorder being an early manifestation in 25% of cases (Cosci *et al.* 2015). However, few studies have addressed the specific issue of the prevalence of various other psychiatric symptoms (besides depression) in patients with CD. Exposure to high levels of endogenous glucocorticoids over a long time leads to changes in brain morphology. Cerebral atrophy, especially in the hippocampus, is highly prevalent in CS. In this case, no strong evidence of structural changes in the central nervous system were identified. This might explain the significant improvement of the patient's physical and mental symptoms after resection of the pituitary microadenoma.

Generally, severe cognitive impairments and affective disorders are often irreversible, and psychiatric symptoms may persist after tumor resection. Moreover, studies have shown that health-related quality of life (HRQoL) is severely impaired in CD patients, especially during the active phase of the disease (Webb *et al.* 2008). Even after treatment and remission of symptoms, HRQoL remains poor (Lindsay *et al.* 2006). Researchers suggested this might be related to the continued physical and mental symptoms of the patients, who require sustained long-term medication and repeated assessment7, (Webb *et al.* 2018). At various stages of CD, mood disorders are associated with increased mortality rates8, (Cosci *et al.* 2015). Early treatment is very important for improving the HRQoL of patients with CD. In addition, long-term regular follow-up of the patient's postoperative psychiatric symptoms is necessary. To continuously improve HRQoL, patients need to undergo regular reviews of relevant indicators, continue to take antipsychotics, and be provided with multidisciplinary treatment.

During the active CD period, anti-depressants and anti-anxiety drugs, such as clozapine, mifepristone, and risperidone, can be used to relieve severe mental symptoms (Santos *et al.* 2017).When using these drugs, the patient's body weight, lipid and glucose levels,

Tab. 3. Serum cortisol and ACTH circadian rhythms

	Plasma cortisol (nmol/L)			ACTH (pmol/L)		
	8am	4pm	12am	8am	4pm	12am
2017-09-12	1420	922.3	838.7	22.94	19.5	14.72
2017-10-30	1810	1421	1345	25.31	22.34	20.53
2017-11-22	1239.29	965.24	401.09	9.44	7.73	2.99
2018-03-01	17.98	72.51	<13.79	2.02	1.22	<1.11
2019-06-18	176.11	81.44	31.25	4.24	2.580	<1.11

and side effects (such as extrapyramidal symptoms and increased prolactin levels) should be monitored (Castinetti *et al.* 2009; Fleseriu *et al.* 2012). During the remission period, psychiatric symptoms may persist or improve dramatically. One case report showed that a CD patient gradually recovered after pituitary tumor surgery and even stopped taking psychotropic drug treatment (Rasmussen *et al.* 2015). However, improvement does not necessarily mean complete recovery, and psychiatric symptoms can reappear after successful surgery (Tiemensma *et al.* 2010). Researchers have stressed that mental and/or psychological monitoring and treatment should occur at all CD stages, using a multidisciplinary approach to diagnosis and treatment (Bratek et al 2015; Pivonello *et al.* 2015b). This is especially important when the patient's psychiatric symptoms persist or worsen. Follow-up psychotherapy, as provided to the current patient, can help the patients get used to the impact of CD.

CONCLUSION

We have described a rare case of CD that was masked by psychiatric symptoms. Neuropsychiatric symptoms can precede the onset of CD, making diagnosis challenging. We report this case to remind clinicians to consider the diagnosis of CD in the evaluation of patients with treatment-resistant neuropsychiatric disease.

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