Successful management of a patient with active Cushing’s disease complicated with coronavirus disease 2019 (COVID-19) pneumonia

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Abstract. We provide the details of the successful management of a patient with active Cushing’s disease complicated with coronavirus disease 2019 (COVID-19) pneumonia. The patient was a 27-year-old Japanese female healthcare worker who was scheduled to undergo pituitary surgery for Cushing’s disease. She had been in close contact with an undiagnosed patient infected with COVID-19 and then developed COVID-19 pneumonia. Despite a lack of known risk factors associated with severe COVID-19 infection, the patient’s dyspnea worsened and her respiratory condition deteriorated, as indicated by the need for 7 L/min oxygen supply by mask to maintain her oxygen saturation at >90%. Medical treatment was initiated to control hypercortisolism by the ‘block and replace’ regimen using steroidogenesis inhibitors and hydrocortisone. The COVID-19 pneumonia improved with multi-modal treatment including antiviral therapy. One month later, after a negative severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) test result and with appropriate protection against virus transmission to medical staff in the operating room and daily medical care nurses, trans-sphenoidal surgery was performed by our highly experienced pituitary surgeon. One month after the surgery, the patient’s basal ACTH and cortisol levels and urinary free cortisol were all under the detection limit. Surgical remission was expected. Since hypercortisolism due to active Cushing’s disease may worsen a COVID-19 infection, multi-disciplinary management that includes appropriate and prompt treatment strategies is mandatory in such cases.

Key words: Cushing’s disease, Coronavirus disease 2019, COVID-19, Medical management, Block and replace regimen

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-CoV-2) was first reported in late 2019 by the health commissioner of Wuhan city in the Hubei province of China, and it has subsequently spread worldwide. By September 2020, the SARS-CoV-2 infection of >80,000 people in Japan had been reported. In the absence of clinical trials to guide the appropriate management of patients with endocrine disorders during the COVID-19 pandemic, several recommendations from the relevant Societies have been reported [1–4].

Here, we report a rare case of the successful management of a patient with Cushing’s disease complicated with COVID-19 pneumonia.

Case Report

A 27-year-old Japanese female healthcare worker had
had amenorrhea (treated with low-dose estrogen/progestin preparations) and dyslipidemia for 6 years. At the same time, she had acne, facial plethora, and a gradual 10-kg weight gain. After transferring from one workplace to another, she visited a new gynecologist who examined her hormonal status. Thyroid dysfunction was suspected because her TSH, fT3, and fT4 levels were 0.78 μIU/L (normal: 0.5–5.0), 2.01 pg/mL (2.3–4.3), and 0.75 ng/dL (0.9–1.7), respectively. She was referred to the Endocrinology Department. On examination, her height, body weight, and body mass index were 154.5 cm, 65 kg, and 27.2 kg/m², respectively. She had high blood pressure (146/90 mmHg) and overt clinical features of Cushing’s syndrome, including full moon face with acne and facial plethora, central obesity, buffalo hump, red skin striae on the abdomen, and multiple subcutaneous hemorraghes on the extremities. Her family history was noncontributory except for Graves’ disease in a cousin. She had no history of smoking or drinking.

The patient’s laboratory findings are provided in Table 1. She had mild fatty liver, normokalemia, and normal glucose tolerance. Her morning and midnight cortisol levels (measured by an electrochemiluminescence immunnoassay, i.e., the Roche Elecsys Cortisol II kit, Roche Diagnostics, Tokyo) were 21.4 μg/dL and 21.1 μg/dL, respectively. The plasma ACTH level was 37.8 pg/mL, and her 24-hr excretion of urinary free cortisol (UFC: measured by a radioimmunoassay, i.e., the Cortisol Kit ‘FR’, Fujirebio, Tokyo) was 473.4 μg/day. Although low-dose dexamethasone (0.5 mg) did not suppress her cortisol level (17.2 μg/dL), high-dose dexamethasone (8 mg) suppressed the morning cortisol level (2.1 μg/dL). Corticotropin-releasing hormone provocation increased her ACTH levels from 75.2 to 130 pg/mL and her cortisol levels from 26.3 to 42.1 μg/dL.

Magnetic resonance imaging (MRI) of the head demonstrated a 5-mm-dia. pituitary mass (Fig. 1a, b). The preoperative diagnosis was active ACTH-secreting pituitary microadenoma, and trans-sphenoidal surgery was scheduled. The levels of other pituitary hormones were within normal limits. The clinical course is shown in Fig. 2. Metyrapone (500 mg/day) was started to counteract the patient’s hypercortisolism before surgery. A few days later, she had close contact with an undiagnosed patient infected with COVID-19 in the hospital ward.

A few days later the patient experienced a fever at 38°C, nausea, and headache. Hydrocortisone (15 mg/day) was added to prevent adrenal insufficiency, but her serum cortisol level was as high as 22.3 μg/dL. She continued to have a 39°C fever and had developed dyspnea. On the 6th day of fever, her arterial oxygen saturation value in the room air had decreased to 90%, and chest radiography and computed tomography (CT) showed

### Table 1

| Blood biochemistry                      |
|-----------------------------------------|
| Aspartate transaminase                  | 27 | U/L |
| Alanine transaminase                    | 41 | U/L |
| γ-glutamyl transpeptidase               | 26 | U/L |
| Total protein                           | 6.0 | g/dL |
| Albumin                                 | 4.0 | g/dL |
| Blood urea nitrogen                     | 11.8 | mg/dL |
| Creatinine                              | 0.61 | mg/dL |
| Sodium                                  | 141 | mEq/L |
| Potassium                               | 3.6 | mEq/L |
| Chloride                                | 105 | mEq/L |
| Total cholesterol                       | 223 | mg/dL |
| Triglyceride                            | 136 | mg/dL |
| Glucose                                 | 89  | mg/dL |
| Hemoglobin A1c                          | 5.6  | % |

| Blood cell counts                       |
|-----------------------------------------|
| Red blood cells                         | 423 | 10⁴/μL |
| Hemoglobin                              | 14.4 | g/dL |
| Platelets                               | 21.0 | 10⁴/μL |
| White blood cells                       | 6.020 | /μL |
| Neutrophils                             | 73.5 | % |
| Eosinophils                             | 0.2  | % |
| Basophils                               | 0.2  | % |
| Lymphocytes                             | 19.8 | % |
| Monocytes                               | 6.3  | % |

| Urine analysis                          |
|-----------------------------------------|
| Protein                                 | ± |
| Glucose                                 | – |
| Ketone                                  | – |

| Endocrinological examination           |
|-----------------------------------------|
| TSH                                     | 0.78 | μIU/mL |
| Free T3                                 | 2.01 | pg/mL |
| Free T4                                 | 0.75 | ng/dL |
| GH                                      | 0.36 | ng/mL |
| IGF-1                                   | 166  | ng/mL |
| PRL                                     | 11.79 | ng/mL |
| LH                                      | 1.85  | mIU/mL |
| FSH                                     | 4.03  | mIU/mL |
| Estradiol                               | 34  | pg/mL |
| DHEA-S                                  | 446 | μg/dL |
| Urinary free cortisol                   | 473.4 | μg/day |

| Diurnal variation                       |
|-----------------------------------------|
| 0800 h                                  | 2300 h |
| ACTH                                    | 37.8 | 68.1 | pg/mL |
| Cortisol                                | 21.4 | 21.1 | μg/dL |

DHEA-S, dehydroepiandrosterone sulfate.
consolidation and interstitial shadows of bilateral lungs (Fig. 1c, e, f); the result of a polymerase chain reaction (PCR) test using her sample on a nasopharyngeal swab was positive for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). She was hospitalized for COVID-19 pneumonia. At that time, no treatment for COVID-19 had been established.

Favipiravir, nafamostat, heparin, and ciclesonide were administered to treat the patient’s SARS-CoV-2 infection. Sulfamethoxazole-trimethoprim was administered to prevent opportunistic Pneumocystis jirovecii pneumonia. On the 7th day after the pneumonia’s onset, the patient’s oxygenation, dyspnea, and productive cough had worsened; she required oxygen administration at 7 L/min by face mask to maintain her oxygen saturation at >90%. Chest radiography showed expanded consolidation (Fig. 1d). The pertinent laboratory findings when the patient’s condition worsened on the 10th day of onset showed an increased white blood cell count (12,500/μL with neutrophils: 93.2%) and increased levels of C-reactive protein (17.3 mg/dL) and procalcitonin (0.23 mg/dL). The D-dimer level (0.27 μg/mL) was within the reference range, and the patient had no abnormalities in the coagulation test except for an increased fibrinogen concentration (776 mg/dL).

The dose of metyrapone was increased to 1,000 mg/day (administered 4×/day after each meal; 08:00, 12:00, 18:00 and before sleep at 21:00), and the dose of hydrocortisone was increased to 30 mg/day (administered 2×/day after meals; 08:00, 18:00). The metyrapone dose was further increased to 4,000 mg/day, and trilostane 240 mg/day (administered 4×/day after each meal; 08:00, 12:00, 18:00 and before sleep at 21:00) was added to control the patient’s UFC and serum cortisol levels (measured by a chemiluminescence immunoassay, i.e., the Cortisol-Abbott (Architect) kit, Abbott Japan, Tokyo during the patient’s hospitalization at 06:00). Respiratory failure improved from the 11th day of onset.

With the control of her hypercortisolism, the patient’s blood pressure also improved to 109/65 mmHg. She experienced side effects of metyrapone: gastrointestinal upset, nausea, dizziness, edema, increased acne, and

Fig. 1  T1-weighted MRI of the patient’s sellae scanned with gadolinium enhancement: sagittal (a) and coronal (b) sections. The pituitary gland shows inhomogeneous enhancement. Chest radiography and CT of the chest at the diagnosis of COVID-19 pneumonia (c, e, f) and on the 10th day of the patient’s hospital stay (d).
hypokalemia. It was difficult to control her hypercortisolism with a reduced tolerable dose of metyrapone for a prolonged period. She was eager to return her job as a healthcare worker. The prevalence of COVID-19 had decreased in her locality at that time.

One month after the patient’s discharge from the hospital, a negative SARS-CoV-2 result obtained by the loop-mediated isothermal amplification (LAMP) method was confirmed. Her surgery was then performed with appropriate protection against the transmission of any virus to the medical staff in the surgery room and the nurses providing the patient’s daily medical care. The tumor was soft and spread widely in the sellae. The border of normal pituitary tissue was partially unclear in a fibrous or infiltrative form. The tumor was therefore removed with a small margin of normal tissue. Invasion into the right cavernous sinus was also evident, and the invasion was radically removed by opening the dura covering the sinus. The 5-mm-dia. low-intensity area that was detected by preoperative MRI was observed to be an old hematoma.

Pathological findings showed a densely granulated corticotroph adenoma with the Ki-67 labeling index of 5.9% (Fig. 3a–d). The tumor grade was considered to be 2b, invasive and proliferative, which may indicate a high risk of recurrence [5]. Immunostaining for somatostatin receptor subtype 5 (SSTR5) was positive with membranous reactivity (Fig. 3e, f).

Postoperatively, the patient had no surgical complications (such as cerebrospinal fluid leakage) or infection except for transient diabetes insipidus. One month after the surgery, her basal ACTH and cortisol levels and UFC were all under the detection limits. Her Cushing’s disease was considered to be in biochemical remission.

**Discussion**

We have provided the details of a patient with COVID-19 pneumonia that was identified shortly after the diagnosis of Cushing’s disease. Despite the lack of known risk factors associated with severe COVID-19 infection, the patient’s respiratory condition deteriorated. Her COVID-19 pneumonia improved with multiple modalities including antiviral therapy and medical treat-
ment to control hypercortisolism by the ‘block and replace’ regimen. One month later, the trans-sphenoidal pituitary surgery was successful.

COVID-19, the pandemic disease caused by SARS-CoV-2, has been associated with higher risks of respiratory failure and admission to the ICU and/or death, especially in patients with comorbidities such as chronic obstructive pulmonary disease, hypertension, diabetes mellitus, malignancy, congestive heart failure, and immunodeficiency syndromes. Older age, current smoker status, and obesity (BMI $\geq 30$ kg/m$^2$) were also reported as risk factors for adverse outcomes of COVID-19 [6-8]. At present, there are no available data regarding the behavior of COVID-19 in patients with Cushing’s syndrome. However, the metabolic and other complications associated with Cushing’s syndrome are likely to result in a poor prognosis [2, 9].

Patients with Cushing’s syndrome may be susceptible to severe pneumonia due to changes in the white blood cell count and function secondary to endogenous glucocorticoid excess [10]. Since Cushing’s disease is a condition frequently associated with androgen excess in females, it can be speculated that these patients might have a higher expression of transmembrane serine protease 2 (TMPRSS2), which is an essential component for the activation of the spike protein of SARS-CoV-2 [11], consequently increasing the risk of COVID-19 infection. Moreover, both Cushing’s syndrome and severe COVID-19 are associated with hypercoagulability, and thus patients with active Cushing’s syndrome might be at an increased risk of thromboembolism with COVID-19 [12]. It is recommended that treatment with low-molecular-weight heparin be administered, especially in patients with moderate to severe disease [2, 3], as in our patient. Since opportunistic fungal infections may cause morbidity and mortality in profoundly immunocompromised patients with severe Cushing’s syndrome, sulfamethoxazole-trimethoprin was administered to our patient [3, 13].

Medical therapy to resolve hypercortisolism should be performed not only to avoid the risk of disease progression but also for rapidly ameliorating hypercoagulability and immunosuppression. It was reported very recently that the use of dexamethasone may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death in patients with severe and critical COVID-19 [14]. A prospective meta-analysis of clinical trials of critically ill patients with COVID-19 indicated that the administration of systemic corticosteroids was associated with lower 28-day all-cause mortality [15]. The World Health Organization (WHO) recommends systemic corticosteroids to treat patients with severe and critical COVID-19, and the WHO issued a conditional recommendation not to use corticosteroid therapy in patients with non-severe COVID-19 [16].

Our patient was diagnosed with moderate COVID-19 pneumonia, since she did not require admission to the ICU or mechanical ventilation. We worried about the possible prolongation of virus elimination by high-dose corticosteroid administration. In addition, firm evidence of benefits of steroid treatment had not been established when this patient was treated. The optimally controlled cortisol levels in patients with Cushing’s disease complicated with COVID-19 remain to be determined.

The steroidogenesis inhibitor metyrapone has a rapid

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**Fig. 3** Histopathology of the pituitary adenoma: densely granulated corticotroph adenoma. Hematoxylin & cosin staining showed the solid growth of tumor cells with basophilic cytoplasm (a). Immunohistochemistry for ACTH showed diffuse cytoplasmic reactivity (b). The Ki-67 index was 5.9% (c). Immunostaining for low-molecular-weight cytokeratin (CAM5.2) showed the perinuclear pattern (d). The immunostaining for SSTR2 was negative, and that for SSTR5 was membranous-positive (e, f).
effect and reversibility. A retrospective study reported the outcomes of 195 patients with hypercortisolism (including 115 patients with Cushing’s disease) who were treated with metyrapone [17]; metyrapone monotherapy administered before surgery for an average of 4.0 months significantly improved the biochemical targets, and the mean total daily dose for patients with Cushing’s disease was reported to be 1,380 mg (range: 500–3,500 mg). Our patient needed as much as 4,000 mg of metyrapone combined with a competitive inhibitor of 3β-hydroxysteroid dehydrogenase (i.e., trilostane) to completely inhibit cortisol production, since another steroidogenesis inhibitor, ketoconazole, has not been approved for Cushing’s syndrome in Japan. In comparison to metyrapone (which must be administered ≥4×/day), a recent study indicated that osilodrostat is effective in controlling Cushing’s disease by twice-daily administration [18].

The block and replace regimen may reduce the risk of iatrogenic adrenal insufficiency. Although the number of practical descriptions of adjusting doses of drugs is insufficient [3, 13], the block and replace regimen is commonly used in Japan when high doses of steroid inhibitors are provided in an emergency setting. Diurnal cortisol curves and the UFC excretion are useful markers for assessing hypercortisolism. Although a liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assay is recommended during a patient’s metyrapone treatment, cortisol immunoassays may cross-react with 11-deoxycortisol and other metabolites [19]. Moreover, supplementation with hydrocortisone may result in overestimations of the 24-hr UFC and serum cortisol levels, depending on the timing. Dexamethasone can be useful given no interference with the measurement of serum cortisol and UFC. Based on the results of the immunoassays, we concluded that our patient’s endogenous steroids were not sufficiently suppressed during the metyrapone dose adjustment, and we have continued the 30-mg hydrocortisone supplementation. Fortunately, her pneumonia improved relatively early and the dose of hydrocortisone was not increased.

In our patient’s case, the maximum tolerable dose of metyrapone was not enough to resolve her hypercortisolism, but her 24-hr UFC decreased to the normal range after the addition of trilostane. We cannot exclude the possibility of a delayed response to metyrapone, since trilostane was administered 3 days after the start of the increased dose of metyrapone (4,000 mg/day). The usefulness of trilostane combination therapy should be investigated with the use of possible biomarkers such as serum potassium and 11-deoxycorticisone to demonstrate the suppressed enzyme activities.

There are several possible explanations for our patient’s resistance to metyrapone. First, 11-deoxycortisol and supplemented hydrocortisone may interfere with the 24-hr UFC and serum cortisol levels as noted above, but we did not measure the serum 11-deoxycortisol concentration during the patient’s metyrapone therapy. Secondly, although medications administered to treat COVID-19 pneumonia have not been reported to interact with metyrapone, they may interfere with other steroids and steroidogenesis inhibitors, since ritonavir is known to inhibit cytochrome P450A (CYP3A) enzyme and increase the exposure to corticosterone [20]. Thirdly, immune dysregulation is associated with COVID-19 [21]. The action of proinflammatory cytokines resulted in the activation of the hypothalamus-pituitary-adrenal (HPA) axis, although at a later phase, critical illness-related corticosteroid insufficiency [22] may occur, and SARS-CoV-1 has been known to affect the HPA axis, causing transient hypocortisolism [23]. Finally, genetic differences in the steroidogenic enzymes might account for inter-individual variations in the responsiveness to adrenal-blocking agents, since the therapeutic responses to metyrapone or ketoconazole in patients with Cushing’s syndrome are associated with a polymorphism in the CYP17A1 gene [24].

However, we observed that Crook’s hyaline change—which is a reversible phenomenon observed in corticophroph cells under the influence of high cortisol levels—was relatively mild and obscure in our patient’s low-molecular-weight cytokeratin (CAM5.2) immunostaining. We speculate that the patient’s preoperative hypercortisolemia was under control.

Surgery is the first-line treatment for all causes of Cushing’s syndrome, but during the current pandemic a delay might be appropriate in order to reduce the hospital-associated risk of COVID-19, any post-surgical immunodepression, and thromboembolic risks [1-3]. We thus propose that trans-sphenoidal pituitary surgery should be delayed when possible, because this procedure results in aerosol formation which conveys a high risk of viral transmission [25]. In our patient’s case, a negative SARS-CoV-2 result was confirmed and appropriate protection for all medical staff enabled us to perform a safe operation and postoperative care.

In our patient, the postoperative ACTH and cortisol levels were undetectable, and surgical remission is expected. Since hypercortisolism due to active Cushing’s disease may enhance the severity of COVID-19 infection, it is necessary to provide appropriate, multidisciplinary and prompt treatment.

Ethical Standard

This article does not contain any studies with human
or animal subjects performed by the any of the authors. The identity of the patient has been protected. The patient provided informed consent for this manuscript.

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Disclosure

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