Endocrinology, Diabetes & Metabolism CASE REPORTS

J M K de Filette and others | COVID-19 and Cushing's disease

ID: 21-0182; February 2022
DOI: 10.1530/EDM-21-0182

COVID-19 and Cushing's disease in a patient with ACTH-secreting pituitary carcinoma

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Summary

The pandemic caused by severe acute respiratory syndrome coronavirus 2 is of an unprecedented magnitude and has made it challenging to properly treat patients with urgent or rare endocrine disorders. Little is known about the risk of coronavirus disease 2019 (COVID-19) in patients with rare endocrine malignancies, such as pituitary carcinoma. We describe the case of a 43-year-old patient with adrenocorticotrophic hormone-secreting pituitary carcinoma who developed a severe COVID-19 infection. He had stabilized Cushing's disease after multiple lines of treatment and was currently receiving maintenance immunotherapy with nivolumab (240 mg every 2 weeks) and steroidogenesis inhibition with ketoconazole (800 mg daily). On admission, he was urgently intubated for respiratory exhaustion. Supplementation of corticosteroid requirements consisted of high-dose dexamethasone, in analogy with the RECOVERY trial, followed by the reintroduction of ketoconazole under the coverage of a hydrocortisone stress regimen, which was continued at a dose depending on the current level of stress. He had a prolonged and complicated stay at the intensive care unit but was eventually discharged and able to continue his rehabilitation. The case points out that multiple risk factors for severe COVID-19 are present in patients with Cushing's syndrome. 'Block-replacement' therapy with suppression of endogenous steroidogenesis and supplementation of corticosteroid requirements might be preferred in this patient population.

Learning points:

- Comorbidities for severe coronavirus disease 2019 (COVID-19) are frequently present in patients with Cushing's syndrome.
- 'Block-replacement' with suppression of endogenous steroidogenesis and supplementation of corticosteroid requirements might be preferred to reduce the need for biochemical monitoring and avoid adrenal insufficiency.
- The optimal corticosteroid dose/choice for COVID-19 is unclear, especially in patients with endogenous glucocorticoid excess.
- First-line surgery vs initial disease control with steroidogenesis inhibitors for Cushing's disease should be discussed depending on the current healthcare situation.

Background

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a significant impact on the health care systems to date. The clinical presentation of coronavirus disease 2019 (COVID-19) is diverse, ranging from asymptomatic illness to respiratory failure requiring admission to the intensive care unit (ICU). Risk factors for severe course include old age, male gender, comorbidities such as arterial hypertension, diabetes mellitus, chronic lung-, heart-, liver- and kidney disease, malignancy, immunodeficiency and pregnancy (1). Little is known

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about the risk of COVID-19 in patients with rare endocrine malignancies, such as pituitary carcinoma.

Case presentation

This case concerns a 43-year-old man with adrenocorticotrophic hormone (ACTH)-secreting pituitary carcinoma (with cerebellar and cervical drop metastases) with a severe COVID-19 infection. He had previously received multiple treatment modalities including surgery, radiotherapy, ketoconazole, pasireotide, cabergoline, bilateral (subtotal) adrenalectomy and temozolomide chemotherapy as described elsewhere (2). His most recent therapy was a combination of immune checkpoint inhibitors consisting of ipilimumab (3 mg/kg) and nivolumab (1 mg/kg) (anti-CTLA-4 and anti-PD-1, respectively) every 3 weeks for four cycles, after which maintenance therapy with nivolumab (240 mg) every 2 weeks was continued. Residual endogenous cortisol production was inhibited with ketoconazole 800 mg daily. He had stabilized disease with a decrease in plasma ACTH, urinary free cortisol and stable radiological findings (2). Surgical resection of the left adrenal remnant was planned but was not carried out due to the development of a COVID-19 infection.

In March 2021, he consulted our emergency department for severe respiratory complaints. He had been suffering from upper respiratory tract symptoms for one week, with progressive dyspnoea in the last three days. He tested positive for SARS-CoV-2 the day before admission. On examination, his O_2 saturation was 72%, with tachypnoea (40/min) and bilateral pulmonary crepitations. His temperature was 37.2°C, blood pressure 124/86 mmHg and pulse rate 112 bpm. High-flow oxygen therapy was initiated but yielded insufficient improvement (O_2 saturation of 89% and tachypnoea 35/min). He was urgently intubated for respiratory exhaustion.

Investigation

Initial investigations showed type 1 respiratory insufficiency with PaO_2 of 52.5 mmHg (normal 75–90), $PaCO_2$ of 33.0 mmHg (normal 36–44), pH of 7.47 (normal 7.35–7.45) and a P/F ratio of 65.7 (normal >300). His inflammatory parameters were elevated with C-reactive protein level of 275.7 mg/L (normal <5·0) and white blood cell count of 7.1 × 10^9 per L with 72.3% neutrophils. His most recent morning plasma ACTH-cortisol level (measured using the Elecsys electrochemiluminescence immunoassays on a Cobas 8000 immunoanalyzer [Roche Diagnostics]) before his admission was 213 ng/L (normal 7.2–63) and 195 µg/L (normal 62–180) respectively, while a repeat measurement 3 weeks after his admission demonstrated increased cortisol levels of 547 µg/L (possibly iatrogenic due to treatment with high-dose hydrocortisone) and a decreased ACTH of 130 ng/L.

Treatment

On admission, he was started on high-dose dexamethasone therapy for 10 days together with broad-spectrum antibiotics for positive sputum cultures containing *Serratia*, methicillin-susceptible *Staphylococcus aureus* and *Haemophilus influenzae*. Thromboprophylaxis with an intermediate dose of low molecular weight heparin (tinzaparin 14 000 units daily for a body weight of 119 kg) was initiated. A 'block-replacement' regimen was adopted with the continuation of ketoconazole (restarted on day 11) in view of his endocrine treatment and the supplementation of hydrocortisone at a dose depending on the current level of stress. The consecutive daily dose of hydrocortisone and ketoconazole is shown in Fig. 1.

Outcome and follow-up

He developed multiple organ involvement, including metabolic acidosis, acute renal failure requiring continuous venovenous hemofiltration, acute coronary syndrome type 2, septic thrombophlebitis of the right jugular vein, and critical illness polyneuropathy. He was readmitted twice to the ICU, for ventilator-associated pneumonia and central line-associated bloodstream infection respectively. He eventually recovered and was discharged from the hospital to continue his rehabilitation.

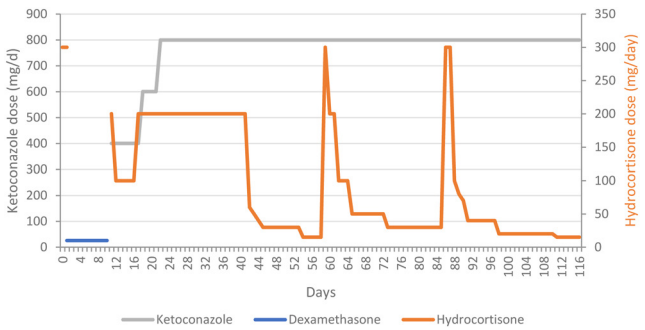

Figure 1
'Block-replacement' therapy with ketoconazole and hydrocortisone/dexamethasone. Dexamethasone 10 mg daily was initially started as COVID-19 treatment, followed by hydrocortisone at a dose consistent with current levels of stress. Ketoconazole was restarted on day 11 and titrated to a dose of 800 mg daily to suppress endogenous glucocorticoid production.

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Discussion

We describe the case of a patient with severe COVID-19 infection with active Cushing's disease due to pituitary carcinoma, who was treated with high-dose dexamethasone followed by 'block-replacement' therapy with hydrocortisone in combination with off-label use of ketoconazole as a steroidogenesis inhibitor. His hospitalization was prolonged by multiple readmissions to the ICU for infectious causes. Our case illustrates the presence of multiple comorbidities for a severe and complicated course of COVID-19 in a patient with active Cushing's disease.

Dexamethasone was initially chosen as the preferred corticosteroid therapy, in analogy with the RECOVERY trial, in which dexamethasone at a dose of 6mg once daily (oral or i.v.) resulted in lower 28-day mortality in hospitalized patients with COVID-19 requiring oxygen therapy or invasive mechanical ventilation (3). However, the optimal dose/choice of corticosteroid therapy is unclear, especially in a patient population with pre-existing hypercortisolaemia. A similar survival benefit for hydrocortisone compared to dexamethasone has yet to be convincingly demonstrated. This may be explained by differences in anti-inflammatory activity but could also be due to the fact that recent studies with hydrocortisone were stopped early and were underpowered (4, 5).

Multiple risk factors for a complicated course of COVID-19 are present in patients with Cushing's syndrome and might increase morbidity and mortality (6, 7). These include a history of obesity, arterial hypertension and impaired glucose metabolism. Prevention and treatment of these pre-existing comorbidities are essential.

Patients with Cushing's syndrome also have an increased thromboembolic risk, which is further accentuated by the development of severe COVID-19 infection (6, 7). Thromboprophylaxis with low molecular weight heparin is associated with lower mortality in COVID-19 patients with high sepsis-induced coagulopathy score or high D-dimer levels (8) and is presently widely used in the treatment of severe COVID-19 disease (9). Subsequently, this treatment is indicated in hospitalized COVID-19 patients with Cushing's syndrome. It is unclear whether therapeutic anticoagulation dosing could provide additional benefits (6, 7). An algorithm based on the International Society on Thrombosis and Hemostasis-Disseminated Intravascular Coagulation score was proposed to evaluate the ideal anticoagulation therapy in severe/critical COVID-19 patients, with an indication for therapeutic low molecular weight heparin dose at a score ≥ 5 (9).

Furthermore, the chronic cortisol excess induces suppression of the innate and adaptive immune response. Patients with Cushing's syndrome, especially when severe and active, should be considered immunocompromised and have increased susceptibility for viral and other (hospital-acquired) infections. Prophylaxis for *Pneumocystis jirovecii* with trimethoprim/sulfamethoxazole should therefore be considered (6, 7).

Additionally, there is a particular link between the pathophysiology of COVID-19 and Cushing's syndrome. The SARS-CoV-2 virus (as well as other coronaviruses) enter human cells by binding the ACE2 receptor. The transmembrane serine protease 2 (TMPRSS2), expressed by endothelial cells, is additionally required for the priming of the spike-protein of SARS-CoV-2, leading to viral entry. TMPRSS2 was studied in prostate cancer and found to be regulated by androgen signalling. Consequently, the androgen excess frequently associated with Cushing's syndrome might be an additional risk factor for contracting COVID-19 via higher TMPRSS2 expression (10), especially in women, in whom the effect of excess androgen would be more noticeable compared to male patients with Cushing's syndrome.

Treating Cushing's syndrome with a 'block-replacement' approach, with suppression of endogenous steroidogenesis and supplementation of corticosteroid requirements, is an approach that should be considered, especially in severe or cyclic disease. The use of this method might decrease the need for monitoring and reduce the occurrence of adrenal insufficiency (7). Our patient was on treatment with ketoconazole, which was interrupted at initial presentation and then restarted under the coverage of a hydrocortisone stress regimen. Ketoconazole was chosen because of its availability. Advantages of ketoconazole over metyrapone include its antifungal activity with the potential for prevention of invasive pulmonary fungal infections, as well as its antiandrogen action (especially in female patients) and subsequent inhibition of TMPRSS2 expression (10). Regular monitoring of the liver function (every month for the first 3 months, at therapy initiation or dose increase) is necessary. Caution is needed due to its inhibition of multiple cytochrome P450 enzymes (including CYP3A4) and subsequently greater risk of drug-drug interactions vs metyrapone (7, 10). Another disadvantage of ketoconazole is the need for oral administration. In our patient, ketoconazole was delivered through a nasogastric tube. i.v. etomidate is an alternative in case of an unavailable enteral route.

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Finally, as a general point, the first-line treatment of a patient with a novel diagnosis of Cushing's disease is transsphenoidal surgery. Recent endocrine recommendations pointed out the possibility of initial disease control with steroidogenesis inhibitors in patients without an indication for urgent intervention during a high prevalence of COVID-19 (7). This would allow the optimalization of metabolic parameters; emphasizing that the short-to mid-term prognosis is related to the cortisol excess and not its cause. Surgery could then be postponed until the health situation allows for safe elective surgery (7). This decision depends of course on the evolution of COVID-19 and the healthcare system in each country and should be closely monitored by policymakers and physicians.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Patient consent
Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Author contribution statement
J M K de Filette is an endocrinologist-in-training and was the main author. All authors were involved in the clinical care of the patient. All authors contributed to the reviewing and editing process and approved the final version of the manuscript.

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Received in final form 10 January 2022
Accepted 9 February 2022