A Young Man Suspicious for Cushing's Syndrome With Coronavirus Disease-19 (COVID-19): A Case Report

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Abstract- The 2019 global Coronavirus syndrome pandemic (COVID-19) has entered more than two hundred countries around the world, involving <82 million persons and >1,800,000 deaths (until January, 1st 2021). We report on COVID-19 infection in the context of a Cushing's syndrome (CS) from Iran. A 36-year-old man with proximal myopathy, plethora, and striae with central obesity was evaluated for Cushing's syndrome. During the high dose dexamethasone test, the patient developed symptoms of cough, low-grade fever, and weakness then was admitted to the ICU with a diagnosis of COVID-19. Despite treatment according to national protocols for COVID-19, the patient unfortunately died. In this report, we intend to discuss the various aspects of Cushing's syndrome and severe COVID-19 infection.

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Keywords: Coronavirus disease (COVID-19); Cushing's syndrome; Immunosuppression

Introduction

In December 2019, a novel coronavirus, being the third extremely infective CoV and called coronavirus disease 2019 (COVID-19) in the city of Wuhan, was confirmed by the World Health Organization (1). COVID-19's clinical presentation range is heterogeneous, progressing from flu-like syndrome to acute pneumonia, never rarely contributing to acute respiratory distress syndrome, and needing intensive care support. No specific drug for the treatment of SARS-CoV-2 is currently recommended (2). There are reports documenting the low-to-moderate dose usage of corticosteroids in serious patients with coronavirus disease (3). Antiviral, antimalarial, and monoclonal antibodies attacking the IL-6 pathways are other therapies. SARS-CoV-2 uses ACE2 as a receptor to penetrate the pneumocytes and is found in different tissues, such as the adrenal and pituitary glands (4). Autopsy experiments of people who died after the 2003 SARS epidemic have demonstrated that the virus has direct cytotoxicity on the adrenal glands. People with diabetes, overweight, malnutrition, adrenal insufficiency, and CS may be seriously impaired by COVID-19 infection (5). In specific, the European Society of Endocrinology (ESE) has launched a new declaration and a set of specialist reference points as a therapeutic reference on the treatment of endocrine disorders in the context of the COVID-19 pandemic (6). In CS patients, high BMI, hypertension, insulin resistance or diabetes, proximal muscle wasting and fatigue, and infection vulnerability are widely done. The primary cause of mortality in CS patients is heart disease, and the risk of coronary and cerebrovascular incidents is higher than that of the wider public (7).

At the physiological level, glucocorticoids induce immune-enhancing effects in healthy people in the primary stage of infection with priming risk sensor and cytokine receptor activity, sensitizing the immune response to foreign agents (8). However, glucocorticoid excess state can cause severe immunosuppression, with impairment of innate and adaptive immune systems. Consequently, as the persistent glucocorticoids excess, the number of B and T lymphocytes will be decreased (9).

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This reduces the number of B and T lymphocytes and inhibits the function of T helper cells, and then disrupts the rapid response to foreign agents such as viruses and the targeting of adaptive responses, leading to opportunistic or intracellular infections. According to current data, Cushing's syndrome can be accompanied by an elevated risk of viral infection, on average 21-51% incidence rate. Since there are no guidelines for the treatment of COVID-19 in certain immunocompromised patients, such as Cushing's syndrome, reporting these rare cases can be helpful for decision-making in the future (10). In the current paper, we aim to report an active CS patient with COVID-19 infection.

Case Report

A 36-year-old man was referred to the endocrinologist, suggestive for CS, two weeks before hospitalization with the following signs and symptoms: weight gain, proximal muscle weakness, central obesity, increased supraclavicular and interscapular fat pad, typical striae, easy bruising, plethoric face, and high blood pressure. Due to the most discriminatory features of Cushing's signs, the urinary-free cortisol (UFC) and baseline serum cortisol were requested on an outpatient basis. The 24-h UFC level were 1027 and 1214 (1.5-63 µg/day) for two separate samples, respectively. Then, on an overnight dexamethasone suppression test with 1 mg of drug 8 am, serum cortisol was not suppressed 22.3 (normal range 5-25 µg/dl). About findings confirmed the presents of Cushing's syndrome. To differentiate ACTH-dependent from non-ACTH-dependent Cushing's syndrome, the ACTH-level was requested, which showed high levels of it [80.5 (0.1-46 pg/ml)].

Based on elevated ACTH level, a high dose dexamethasone suppression test was performed to determine the source of excess cortisol production. Urinary free cortisol level after high dose dexamethasone suppression test (23.4 µg/dl) showed more than 90% suppression which strengthened the pituitary origin of cortisol secretion.

However, during the high dose dexamethasone test, the patient developed symptoms of cough, low-grade fever, weakness, and oxygen saturation 8 then was admitted to the ICU with a diagnosis of COVID-19. Due to the patient's serious condition, a pituitary MRI was not possible to perform.

At the time of hospitalization, a venous blood gas (VBG) test taken from the patient showed measures as below, PH: 7.44, PaCO2: 50.5, and HCO3:34.4. To confirm COVID-19, we conducted a chest CT-scan. The pulmonary infection presenting by ground-glass opacity in the medium field, more apparent opacity in the medium-low fields of both lungs.

COVID-19 Reporting and Data System (CO-RADS) for standardized assessment of pulmonary involvement of COVID-19 showed scale IV on non-enhanced chest CT at admission time. In addition, CT scans showed increased adipose tissue in the intraperitoneal, retroperitoneal, retrocorial, epicardial as well as mediastinal spaces (Figure1). According to laboratory test, inflammatory indices [C-reactive protein (CRP) 40 mg/l], lactate dehydrogenase (1083 U/l), ferritin (448 ng/ml) and D-dimer (684 µg/l) showed evaluation on admission time. Vitamin D deficiency was also seen in this case (Table 1). Furthermore, the COVID-19-PCR test became positive after two days.

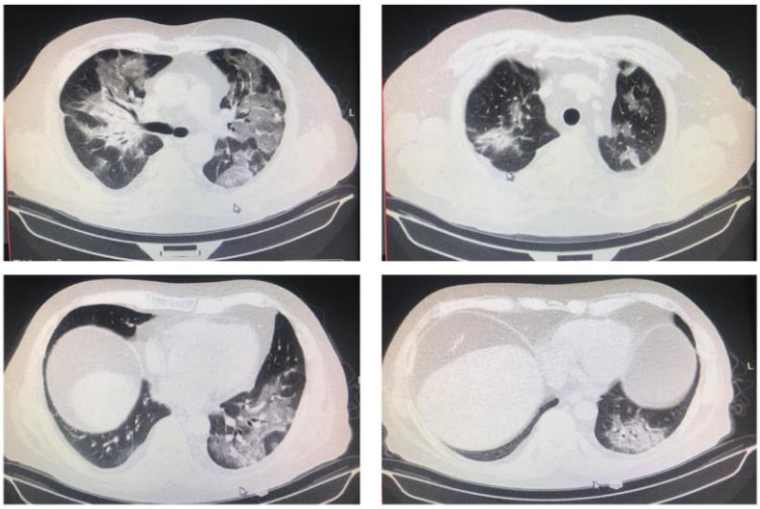

Figure 1. Pulmonary consolidation compatible with COVID-19

Table 1. Laboratory testing results at the time of admission

Blood Test	2020.11.27	2020.11.29	2020.12.2	2020.12.5
White Blood Cells (n.v. 4.00–10.00 10 9/L)	7.3	6.8	3.8	2.2
Red Blood Cells (n.v. 4.60–6.20 10 12/L	4.62	3.12	3.22	3.01
Hemoglobin (n.v. 120–180 g/L)	14.7	11.8	9.9	9.1
Hematocrit (n.v. 0.360–0.520 L/L)	46.2	36.0	31	30.5
Platelets (n.v. 130–450 10 9/L	15.2	152	185	142
Neutrophil (n.v. 1.80–7.80 10 9/L	92.4	92.2	87.4	73.6
Lymphocyte (n.v. 2.00–4.50 10 9/L	3.5	4.4	7.2	23.9
BUN (n.v. 7.00–21. 0 mmol/L	18.6	30.6	56.0	52.0
Creatinine (n.v. 59–104 umol/L)	1.1	1.7	3.0	3.3
Fasting glucose	300	221	198	1401
Sodium (n.v. 136–146 mmol/L	142	137	131	135
Potassium (n.v. 3.5–5.1 mmol/L)	4.1	4.3	4.2	4.6
ALP(n.v. 98–279 U/L)	208	178	268	357
GPT (n.v. 10–38 U/L)	33	48	51	57
GOT (n.v. 10–40 U/L)	23	34	26	25
Lactate dehydrogenase (n. v. 230–460 U/L)	1083	1096	1152	1236
PT(11.5-14.5 sec)	13.9	13.2	13.8	15.2
PTT (24-40 sec)	39	26	43	51
INR (0.8-1.2)	1.1	1.0	1.2	1.2
Bil.T	1.2	0.9	0.8	0.7
Bil.D	0.1	0.2	0.1	0.2
Urine volume (24 hours)	3900			
Urine creatinine (24 hours)	1.1			
Urine protein level (24 hours)	160			
Galactomannan test (Aspergillus Ag) (normal<0.5)	1.67			

Initial hospital care for coronavirus according to Iranian protocol was focused on supportive care and drug treatment, including O_2 therapy, hydroxychloroquine (200 mg for ten days), and dexamethasone (8 mg for two days). Due to increased interleukin 6 to 34.5 (normal range: 0-5.9 pg/ml), remdesivir (200 mg IV stat then, 100 mg/day for four days), and interferon-beta-1α (12 million IU 3 doses every other day) were prescribed. An increased level of procalcitonin to 3.69 (normal <0.5 ng/ml) persuade us to initiate imipenem, vancomycin, and levofloxacin antibiotics to cover bacterial infections.

In the final stages of the treatment course, respiratory stress was created in the patient, suspicious for pulmonary thromboembolism (PTE); hence, CT-angiography was requested, and therapeutic doses of heparin were started. As the patient's condition became worse, methylprednisolone pulse therapy (500 mg for three days) was prescribed.

Twelve hours after intubation, he suffered a drop in blood pressure and septic shock. Then, the patient developed hyperglycemia and received a regular insulin infusion. Eventually, the patient did not respond to any of the treatment modalities and, unfortunately, died.

Discussion

Once a new outbreak has spread around the world, the prior-published clinical protocols may not be adequate and sufficient enough to treat a previous disease. The major challenge in CS treatment superimposed by COVID-19 is the prolonged use of corticosteroids.

Hypertension is usual comorbidity in CS patients, causing the interaction of numerous pathophysiologic mechanisms, comprising glucocorticoid and mineralocorticoid receptors stimulation as well as the related sleep apnea, insulin resistance, and renin-angiotensin system overexpression (11). Moreover, about 40-50 % of Cushing's disease patients have been described to develop diabetes, and about 20-30 % more proportion have impaired glucose tolerance (12,13).

Additionally, active CS patients are at high risk for viral infections, as well as other opportunistic infections, mainly invasive fungal or atypical bacterial infections, which can cause sepsis and an increased rate of mortality. Also, COVID-19 patients, in essence, are at risk of secondary fungal and bacterial infections during hospitalization (14). Therefore, in hospitalize COVID-19 cases with Cushing's disease, prolonged antiviral and broad-spectrum antibiotics therapy with a more accurate approach should be recommended (15).

For entire causes of Cushing's syndrome, surgery is the first-line therapy, but during the COVID-19 coinfection, a delay before surgery could be suitable to decrease the hospital-related risk, any post-surgical

immunosuppression, and thromboembolic events. Thromboembolic events and immunosuppression are prevalent features in CS.

Cortisol-lowering agents, such as metyrapone, ketoconazole, and the new osilodrostat, are commonly effective within hours to days. The etomidate therapy should be temporarily used when urgent cortisol control is needed (14). This patient suffered from septic shock, and ketoconazole was not started. Metyrapone, osilodrostat, and etomidate were not accessible.

When Cushing's syndrome patients are in remission, the risk of infection is significantly reduced; however, the comorbidities associated with hypercortisolism might persist, such as diabetes, hypertension, obesity, and together with thromboembolic events. Since these comorbidities are related to an elevated risk of mortality in patients with COVID-19, Cushing's syndrome patients, even in remission, should be considered as a high-risk group, and suitable self-protection approaches should be conducted to abate the risk of contagion (15).

In conclusion, COVID-19 patients with CS could have particular clinical presentation and complications in active hypercortisolemia state, and so precise monitoring and unique attention should be set to these susceptible and particular patients. Furthermore, these medical therapies should be extended as bridge management while waiting for the reduction of the pandemic.

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