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Teaching Case Series

Challenges in the Management of the Patients With COVID-19 Infected Cushing's Syndrome: Two Cases and Literature Review

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ABSTRACT

Coronavirus disease-2019 (COVID-19) has become a serious health problem in Turkey and the world. The diagnosis stage of many chronic diseases, the treatment process and the status of being affected by COVID-19 have become the focus of attention in the medical community during the pandemic, which has been continuing for nine months. We will discuss the course of COVID-19 infection over a 32-year-old and 76-year-old female patient with Cushing syndrome who applied to our clinic as a tertiary referral centre.

HIGHLIGHTS

In the PUBMED database, we searched the keywords of COVID-19 and Cushing's syndrome, hypercortisolism. We discussed Cushing's disease in the COVID period over our cases and the publications that have the quality of recommendation.

We recommend being more careful when evaluating this group of patients who are considered at high risk for COVID infection, with comorbid diseases such as hypertension and diabetes-referring to relevant centres in case of high suspicion of Cushing syndrome, controlling hypercortisolism during the epidemic process and keeping patients away from hospital environments as much as possible.

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Introduction

COVID-19 infection, which started in China and affected the whole world, is a major pandemic that has become a global problem. In addition to more than 4,000,000 deaths since the disease started in December 2019, the increasing prevalence of COVID-19 in endocrine disorders constitutes a severe health problem.[1]

Since it is a newly identified virus, the effect of the disease on the endocrine system is still unknown. Although there are not many cases in the literature, the possible impacts of COVID-19 on the endocrine system are predicted as postviral hypocortisolemia, hypothyroidism, hypokalemia, hypernatremia, hyperprolactinemia, hypogonadism, hypo-hyperglycemia.[2] Cushing syndrome (CS) is one of the essential endocrine diseases. The presence of long-term and high concentrations of glucocorticoids causes a decrease in B lymphocytes, T lymphocytes and helper T cells. This therapy affects the natural and adaptive immune response to infections.[3] Increased incidence of opportunistic infection, frequently encountered in immunosuppression due to CS, creates a particularly severe bacterial and fungal infection.[4] These factors may cause severe COVID-19-related pneumonia in CS.[2] On the other hand, comorbidities such as hypertension, diabetes mellitus (DM), and obesity are common in CS. These comorbidities may contribute to a more severe course of COVID-19.[2,5,6] However, as far as we know, there is not enough data about managing patients with CS infected with COVID-19. Here, we presented two patients with mild and severe forms of CS infected with COVID-19 and reviewed the available literature.

Case Report 1

A 76-year-old female patient presented with complaints of weakness, fatigue, hair loss, easy bruising and headache for two years. She had been diagnosed with hypertension (metoprolol 50 mg/day) and hypothyroidism (levothyroxine 50 mcg/day) 5 years prior. The patient's serum potassium level was 2.9 mmol/L (3.5-5.19 mmol/L), morning and night cortisol levels were 27.7 mcg/dL and 24.2 mcg/dL, respectively. Plasma ACTH level was 184 pg/mL, 24-hour free urine cortisol (UFC) level was 1657.5 mcg/24 h (reference range: 58-405 mcg/24 h). Salivary cortisol level was not measured due to possible COVID-19 positivity. After two days of the 2 mg dexamethasone suppression test, her cortisol level was 6.42 mcg/dL. Pituitary magnetic resonance imaging (MRI) demonstrated a 15x20 mm mass in the pituitary gland. Visual field examination of the patient was normal.

We needed a differential diagnosis so that 76 years old female patient was presented with hypopotassemia suggesting ectopic hypercortisolemia and pituitary adenomas caused by CS were generally small. Therefore, it was planned to be hospitalized the patient. Due to the COVID-19 pandemic, nasal swabs were taken on the first day of the patient's hospitalization in line with the management's decision. SARS-CoV2 PCR result was positive for this patient without any symptoms. After the positive result of the COVID-19 test, the questions written below were waiting for answers:

1. One can continue surveillance of a CS patient with COVID-19 in the hospital or not?
2. One can prescribe antiviral for COVID-19 or not?
3. One can prescribe medication for CS or not?

The first challenge: "Can the surveillance of a CS patient with COVID-19 be continued in the hospital or not?

According to the national COVID-19 guideline published by the Ministry of Health in Turkey, cases with respiratory distress, shortness of breath, and feeding difficulties are evaluated as severe pneumonia and treated in the hospital. Home monitoring is recommended for those with mild to moderate pneumonia, uncomplicated, and asymptomatic patients. Hydroxychloroquine and/or favipiravir treatment can be planned in this group and monitored at home.[7] Being elderly (≥65 years), cancer, chronic obstructive pulmonary disease, cardiovascular disease, hypertension, diabetes mellitus (DM), obesity, and smoking are the risk factors for COVID-19 infection to be more severe. These patients should be followed more closely at home.[7]

In our case, no pneumonia was detected in thorax high-resolution computerized tomography

(HRCT). The patient did not show the symptoms such as fever, cough, loss of smell or taste, etc. and did not develop tachypnea and hypoxia during the three-day hospital follow-up. For this reason, there was no indication for hospitalization of the patient.

The patient's pituitary mass did not compress the optic chiasm, and the visual field examination was normal. Therefore, there was no urgent surgery indication for a pituitary mass. Her blood pressure was regulated by metoprolol. She had no diabetes. Her hypokalemia was held with oral potassium tablets and a potassium-rich diet. Despite hypercortisolemia, the patient was clinically stable in terms of CS. Hypercortisolemia-associated co-morbidities like DM and hypertension should be actively managed, as they are significant risk factors for adverse outcomes from COVID-19.[2,5] It was inappropriate to follow up in the endocrine clinic as isolation could not be provided. The 18F-Fluorodeoxyglucose Positron Emission Tomography (18F-FDG PET) scan and inferior petrosal sinus sampling (IPSS) examinations were planned for the differential diagnosis of hypercortisolemia. Still, further tests could not be performed during the COVID-19 infection. As a result, the inpatient investigations were delayed to protect the healthcare staff and other patients and prevent viral spread. We evaluated all factors and discharged the patient to have the active COVID-19 phase isolated at home.

The second challenge: "Can antiviral treatment for COVID-19 be prescribed or not?"

In the national COVID-19 guidelines, it is stated that asymptomatic PCR-positive patients can be given hydroxychloroquine and/or favipiravir. However, there is no clear opinion on the necessity of providing treatment to asymptomatic immunosuppressive patients.[7]

Antiviral treatment and broad-spectrum prophylactic antibiotic treatment are recommended due to the risks of prolonged viral infection and secondary infection, especially in patients with COVID-19 positive CS who are followed up in hospitals.[6] In our case, with the recommendation of the Department of Infections Diseases of our University Hospital, antiviral treatment was not initiated because the patient was asymptomatic, and there was no COVID-19 pneumonia in HRCT. A close follow-up on the phone was planned for the patient regarding symptom monitoring.

Third challenge: "Can medication for CS be prescribed or not?"

Endogenous hypercortisolemia leads to the development of DM, hypertension and obesity and increases the risk of cardiometabolic complications and cardiac failure. DM, hypertension and obesity are the best-known risk factors for the poor prognosis of COVID-19. For this reason, it is thought that COVID-19 may have a worse prognosis in patients with CS.[2,6]

The reason for acute respiratory distress syndrome in critically ill patients infected with COVID-19 is thought to be a severe cytokine storm in the body. These patients respond well to anti-inflammatory and anti-cytokine treatments.[8] It has been reported that cases who received disease-modifying antirheumatic drugs (DMARDs) therapy due to arthritis during the pandemic. There was no change in the risk of COVID-19 in patients using DMARDs compared to the normal population. These patients did not have serious respiratory tract infections and did not need intensive care.[9] In hypercortisolemia, the natural and adaptive immune responses are reduced. The patient's ability to cope with infections is reduced. From a different point of view, it can be speculated that the clinical picture may be milder in CS since the immune response is suppressed, and COVID-19-positive patients with CS might not have severe cytokine storm.[6] From our point of view, it is impossible to comment on this issue since our patient had no severe COVID-19 infection with lung involvement.

A minimum number of laboratory and imaging tests should be planned to prevent COVID-19 transmission in patients presenting with hypercortisolemia during the pandemic. Diagnostic tests of patients with mild hypercortisolemia should be delayed for 3-6 months, and patients should be evaluated by telephone intermittently.[10] After excluding adrenocortical carcinoma and ectopic CS, urgent surgical therapy is no longer needed unless there are severe compressive symptoms, and the operation can be postponed. Supraorbital craniotomy should be performed instead of transsphenoidal surgery to reduce viral spread.[11]

Cortisol-lowering treatments are primarily recommended for controlling hypercortisolemia in patients with CS who were followed up during the COVID-19 period without surgery.[11] It is thought that the treatment will eliminate the immunosuppression developing secondary to hypercortisolemia and reduce the risk of infection with COVID-19. At this stage, ketoconazole, metyrapone, osilodrostat, and mifepristone can be used in COVID-negative CS.[11] There is no clear recommendation for COVID-19-positive CS patients. Ketoconazole treatment can interact with COVID-19 treatment and increase the effect of QT prolongation. Therefore, it is not recommended for use with COVID-19 therapy.[12] COVID-19 infection is more common in male patients and is more severe. This is thought to be due to the increased androgenic effect on TPRSS2 expression in the bronchial epithelium.[13] By a similar mechanism, metyrapone therapy can increase androgenic precursors in the pathway while blocking cortisol synthesis. It is thought that this situation, in which androgenic activity in the body leads to an increase in TMPRSS2 expression in the lung, may cause a poor prognosis in the covid-associated ARDS clinic.[12] Considering this situation, a good clinical evaluation should be made when metyrapone therapy is given to COVID-19-positive CS patients because of its possible effects.

Adrenal insufficiency (AI) may occur in patients taking hypocortisolemic medications for CS. The patient should be informed about the symptoms of AI and have glucocorticoids for possible insufficiency.[10] If AI develops, the risk of being infected with COVID-19 increases, and the prognosis worsen. Therefore, while the pandemic continues, mild hypercortisolism may be preferred to adrenal crisis, especially in the short term.[10] It can be predicted that AI caused by any treatment may have severe effects on the course of COVID-19 infection. As shown in Table 1, there is very little data on cases followed up due to CS in the literature. The first patient was a 55-year-

Table 1. Summary of the previous published cases of CS infected with COVID-19.

Case report	Age/Sex	CS disease activity	Comorbidities	Presenting features	Treatment	Outcome
Serban et al. (2020) [14]	55 F	Remission with hypoadrenalism	End-stage chronic kidney disease, and malnutrition		Continuous positive airway pressure and hydroxychloroquine	Dead after six day of hospitalization
	77 M	Active hypercortisolism (under metyrapone treatment)	Obesity, hypertension, dyslipidemia		No treatment was given	Discharged
Beretta et al. (2020)[15]	67 M	Active disease (under metyrapone, cabergoline, pasireotide treatment)	Diabetes, dyslipidemia, secondary hypothyroidism	Dry cough, low grade fever, and symptoms of adrenal insufficiency	Azithromycin, ceftriaxone, hydroxychloroquine	Discharged
Our current cases	76 F	New diagnoses CS, active disease	Hypertension, primary hypothyroidism, impaired glucose metabolism	Asymptomatic	Low molecular weight heparin treatment	Discharged
	32 F	Newly operated with ectopic CS for lung origin	Hypertension, obesity, impaired glucose metabolism	Fever, cough, COVID-19 pneumonia	Favpiravir, low molecular weight heparin, convalescent plasma treatment	Discharged

CS: Cushing's syndrome, F: female, M: male.

old woman who had already AI secondary to the treatment for CS. Later, she was hospitalized for COVID-19 pneumonia and died six days after hospitalization despite hydrocortisone infusion therapy.[14] Similarly, a 67-year-old male patient had active hypercortisolemia and was under treatment. This patient was hospitalized for AI, possibly due to a COVID-19 infection.[15] These cases indicate that COVID-19 also may cause a worsening or development of AI in patients with CS.

Cushing patients may not show typical COVID-19 symptoms such as cough and fever because they are immunosuppressive. Therefore patients should be monitored for a more specific discomfort, taste/odor.[6] Quick control of current hyperglycemia and hypertension is recommended, as diabetes, hypertension, and obesity are the best-known risk factors for the poor prognosis of COVID-19.[6] Anti-thrombotic therapy with low molecular weight heparin should be given. The possible thromboembolic risks of Cushing's disease are known. The pathway of thromboembolic events and the importance of anticoagulant therapy in the pathogenesis of COVID-19 have been demonstrated.[2,5] It is known that hypercortisolemia causes prolonged viral infections and the development of opportunistic bacterial and fungal infections.[16] Co-trimoxazole is recommended for Pneumocystis pneumonia (PCP) prophylaxis in cases evaluated as severe CS (spot cortisol >37 mcg/dL or plasma ACTH >100 pg/mL).[17]

The SARS-CoV-2 virus enters the cell membrane through the ACE 2 receptor.[18] This results in hypokalemia with the help of increased activity of the renin-angiotensin-aldosterone system (RAAS) system. The activity of SARS-CoV-2 on RAAS in patients with hypokalemia due to Cushing's disease may lead to a deepening of hypokalemia.[2] This point should also be considered in COVID-19-positive patients with CS.

So, how did we manage the case?

Primarily, we thought that there is a possibility that AI caused by the CS treatment may worsen the severity of the COVID-19 infection. Secondly, it is unknown whether giving cortisol-lowering therapy to a stable patient with CS during the pandemic increases the risk of cytokine storms in the case of COVID-19. Therefore, we did not initiate cortisol-lowering treatment because of our patient's mild form of CS (no severe hypertension or hypokalemia). We prescribed enoxaparin sodium to prevent thromboembolic complications and co-trimoxazole for PCP prophylaxis. The patient had no symptoms other than malaise and fatigue at home. On the 14th day, the SARS-CoV-2 PCR test was negative in the nasal swab. The patient did not accept additional examinations and surgical treatment for CS during the pandemic. Low-dose metyrapone treatment was given for the patient's hypercortisolemia in the long term. Low-dose treatment was preferred due to the possibility of AI in the patient and the difficulty of following the patient during the pandemic. In the literature, similar to our patient, a 71-year-old male was reported with CS who discontinued metyrapone one month ago due to gastrointestinal complaints. Although he had active disease, he recovered after one week of isolation without COVID-19 treatment.[14]

Case Report 2

A 32-year-old female patient was admitted to the endocrinology clinic with the complaint of weight gain, flushing, early bruising, and purple-coloured stretch marks for six months. The patient didn't have any previously diagnosed disease. She was a non-smoker and non-drinker. High blood pressure (190/100 mmHg) and severe hypopotasemia (2.59 mmol/L) were determined. The patient had a baseline cortisol value of 27.5 mcg/dL, an ACTH level of 101 pg/mL, and UFC 1,848 mcg/24 h.

Serum cortisol level was not suppressed with 2 mg and 8 mg dexamethasone tests. IPSS was performed for the differential diagnosis of ectopic CS, which was found to be precisely peripheral ACTH elevation. Lesion scanning was performed considering ectopic CS in the patient with a resistant hypertension clinic and severe hypokalemia. Thoracic CT was performed, and it was observed that the patient had a 22 mm lesion in the left lung. In our centre, an 18F-FDG PET scan is first performed to screen patients with ectopic CS. If the lesion is not detected, the gallium-68 DOTATATE PET scan method is

used. In this patient, an 18F-FDG PET scan was performed, and the same lesion was observed with a high SUV max (11.78) in the left lung. There was no pathological involvement in other organs and systems. The diagnosis of ectopic CS was confirmed in the patient, and left lung lower lobectomy was planned. Due to the COVID-19 pandemic, the SARS-CoV-2 PCR test was performed two times before surgery, and the results were negative. Left lung lower lobectomy was performed for the patient whose pathology was presented as neuroendocrine, and the Ki-67 proliferation index was 2-3%. AI did not develop in postoperative follow-up. No cortisol was suppressed with 1 mg dexamethasone in the first week after surgery, but the UFC level decreased to 156 mcg/24 h. On the other hand, hypertension regulation of the patient was easily achieved with a single agent in the postoperative period, and her hypopotasemia requiring daily high-dose parenteral potassium replacement was resolved entirely. She lost six kilograms within ten days.

The first problem we faced in the post-surgical management of the patient was a non-COVID-19 infection. Approximately three weeks after surgery, she presented with fever, temporary loss of consciousness and chest pain. SARS-CoV-2 PCR test was performed, considering the high probable cause of the COVID-19 pandemic in the patient. COVID-19 was excluded in the patient whose thoracic CT imaging and PCR test were negative. At the same time, other opportunistic causes of infections such as fungal infections were excluded. Especially for PCP, it was ruled out due to the characteristic interstitial pneumonia appearance and lack of increased oxygen demand. Aspergillus infection was removed because there was no cavity known as a fungus ball in thoracic imaging, and serum galactomannan antigen was found to be negative.

Newly developed areas of large emboli were observed in the cranial imaging, which was done due to changes in the consciousness of the patient. Transthoracic echocardiography was performed to find the source of the emboli and revealed vegetations in the mitral valve. The patient was diagnosed with infective endocarditis because of fever, accompanying mitral valve vegetation and areas of septic embolism in both frontal lobes. In the patient's thorax and abdomen CT imaging, septic embolism was also detected in the lungs and spleen. Empirical antibiotic therapy was initiated with the diagnosis of infective endocarditis in the patient with no neurological deficits except temporary confusion. Methicillin-susceptible *Staphylococcus aureus* was grown in blood culture. Surgery planned for approximately 2 cm of vegetation on the mitral and aortic valves was postponed due to the risk of hemorrhagic cerebrovascular events. We planned to give the patient parenteral antibiotic therapy for at least four weeks.

Another problem we faced was giving cortisol-lowering therapy to this COVID-19-positive patient in the event of possible ongoing hypercortisolemia. The reasons might be the lack of AI in the postoperative period and the lack of cortisol suppression with 1 mg dexamethasone in the second week after lung surgery. Whereas serum ACTH, cortisol and two times 24-hour UFC levels were in the normal range. These confounding results were considered due to the patient's active severe infection status and the ongoing very high stress.

The main problem at this stage, in our case, was COVID-19 pneumonia which was added to the complex clinical situation of our patient because of infective endocarditis. SARS-CoV-2 PCR was found to be positive in the patient who was screened for infection in the 3rd week of infective endocarditis treatment due to deterioration in the clinical display of fever and cough. Laboratory and thorax CT were supportive of COVID-19 pneumonia. With the findings, the surgery planned for the valve vegetation could not be performed on the patient who was started treatment for COVID-19 pneumonia. During the pandemic, the immunosuppressive patient who developed COVID-19 pneumonia was started on favipiravir treatment according to the treatment scheme in Turkey (discussed in detail above).[7] Strict control was provided for hypertension and hyperglycemia. She was followed closely in terms of possible hypopotasemia with close electrolyte monitoring. At the same time, due to the increased thromboembolism risk for both CS and COVID-19, the patient was given anticoagulant therapy, which is strongly recommended in the

literature.[11,19] When the patient received treatment for COVID-19 pneumonia, there was no need for oxygen and no organ failure developed in septic condition. Convalescent plasma therapy was also given as there was minimal improvement in the patient's newly developed tachypnea and progression of lung infiltration at the end of antiviral treatment. The valve surgery plan of the patient, whose PCR test became negative on the 10th day after the treatment and whose aggravation was not observed due to COVID-19 pneumonia, came up again. Mitral valve replacement surgery was performed after the SARS CoV-2 PCR test was negative two times in the patient who did not have additional trouble in the follow-up. The PCR sent from the deep tracheal swab during the intubation was positive (approximately four weeks after the first PCR positivity). There was no deterioration in the postoperative clinical condition of the patient due to COVID-19 infection, it was accepted as asymptomatic PCR positivity, and the patient was not given another COVID-19 treatment. The patient was followed up in the isolation unit during this period.

Similar questions to those we discussed in the first case should be asked here as well;

1. Is there an indication for hospitalization and investigation of the aetiology of hypercortisolemia during the pandemic?
2. Surgical or medical treatment in a patient with CS?
3. Should cortisol-reducing therapy be given if mild hypercortisolemia persists in a CS patient with COVID-19 positive and active infective endocarditis?

First challenge: "Is there an indication for hospitalization and investigation of the aetiology of hypercortisolemia during the pandemic?"

In our case, it was decided that the diagnosis stage should not be delayed due to severe hypercortisolemia, resistant hypertension and hypokalemia. The recommendations in the publications regarding the management of CS patients during the COVID-19 pandemic were in this direction.[6,11]

Second challenge: "Surgery or medical treatment in a patient with a diagnosis of CS?"

It was thought that definitive treatment should be performed because the patient had severe hypercortisolemia, resistant hypertension, and profound hypokalemia. On the other hand, the patient's hospital exposure, the increased risk of opportunistic infections and the pandemic brought other problems. Surgery seemed more reasonable because the lesion detected in the lung of our patient could be malignant, lung cancer could not be excluded without a tissue diagnosis, and the location of the lesion was not suitable for diagnostic biopsy. We did not delay the treatment in this case, considering that definitive therapy would be more beneficial for the patient.

Third challenge: "Should cortisol-reducing treatment be given in a CS patient with COVID-19 pneumonia and active period of infective endocarditis in case of ongoing mild hypercortisolemia?"

She might be in remission in terms of CS due to the improvement in blood pressure regulation, hypopotasemia, and weight loss after surgery. However, a re-examination was planned for possible hypercortisolism but could not be performed due to the prolonged active infection status of the patient. AI did not develop during the postoperative period. However, possible hypercortisolism could not be detected due to ongoing complications. Cortisol-lowering therapy could not be started in our patient because its side effects may worsen the course of the infection in the patient with COVID-19.[12] Since it is a new disease and it is not known precisely how it will affect the course of COVID-19, cortisol-lowering treatment was not given to the patient for possible hypercortisolism existing after the lung surgery.

Conclusion

Endocrinologists frequently consider managing patients with CS has been often regarded as highly challenging. At the same time, the increased risk of COVID-19 infection during the pandemic days creates further serious difficulties in disease management. Nevertheless, there is inadequate data to help us in the direction of

these two diseases when they coincide. To the best of our knowledge, very few patients with CS were infected with COVID-19. Table 2 shows the clinical and laboratory features of our cases. Based on our experience, we suggest that differential diagnosis and treatment can be delayed until COVID-19 infection recovers in mild forms of CS. In cases with severe hypercortisolemia, an appropriate method should be followed for a definitive diagnosis and treatment by considering the patient and calculating profit and loss. There is a need for more case-based data on the disease management and selection of therapy in patients with CS during the COVID-19 pandemic.

Table 2. Clinical and laboratory features of our cases.

	Case 1	Case 2
Age / Sex	76-year-old female	32-year-old female
Laboratory values	Baseline serum cortisol: 27.7 mcg/dL ACTH: 184 pg/mL 24-h UFC: 1,657.5 mcg/24h Serum potassium: 2.9 mmol/L (3.5-5.1 mmol/L) Night cortisol: 24.4 mcg/dL 2 mg dexamethasone suppressed cortisol to 16.42 mcg/dL	Baseline serum cortisol; 27.5 mcg dL ACTH: 101 pg/mL 24-h UFC: 1,848 µg/24h Serum potassium: 2.59 mmol/L (3.5-5.1 mmol/L) 2 mg dexamethasone suppressed cortisol to 24 mcg/dL 8 mg dexamethasone suppressed cortisol to 22 mcg/dL
Clinical situation	Hypertension, muscle weakness, impaired glucose metabolism	Resistant hypertension, obesity, impaired glucose metabolism
Imaging examinations	Pituitary MRI: 15x20 mm mass in the pituitary gland	Pituitary MRI: 3 mm mass in the pituitary gland Thorax CT: 2 cm lesion was detected in the left lung 18F-FDG PET scan: 2 cm lesion was detected in the left lung with high SUVmax (11.78).
IPSS	Could not be performed.	Peripheral ACTH secretion was detected.
Diagnosis	Pituitary mass was present, differential diagnosis tests could not be performed.	Ectopic Cushing's syndrome (lung mass) Pathology: neuroendocrine tumor ki-67 index 2-3%
When was COVID-19 diagnosed?	At the time of the first diagnosis	3 weeks after lung mass surgery
How was COVID-19 diagnosed?	PCR positive No pneumonia in thorax CT No symptoms	PCR positive COVID-19 pneumonia in Thorax CT Fever and cough
How was the clinical course of COVID-19?	Asymptomatic PCR positive patient	Infective endocarditis, mitral valve vegetation, septic embolism in the both frontal lobes, lung and spleen (MSSA in the blood culture) and COVID-19 pneumonia
Was treatment given for COVID-19?	No, antiviral treatment was started Low molecular weight heparin treatment	Favipiravir treatment Low molecular weight heparin treatment Convalescent plasma treatment
Was the control SARS CoV-2 PCR test negative?	The 14th day control PCR test was found to be negative.	Oropharyngeal nasopharyngeal swab samples were found to be negative (10th day and 21st day control PCR), Tracheal swab sample (4 weeks after the first PCR positivity).
Has the patient been treated for hypercortisolemia?	Low-dose metyrapone was started in the patient who did not accept re-hospitalization for further examination during the pandemic period.	Lung surgery was performed for ectopic CS. Post-operative hypercortisolemia was evaluated as stress response, no treatment was given.
Last clinical condition	The patient is followed in a stable condition with low dose metyrapone treatment.	She was operated on for mitral valve vegetation. Clinical condition remained stable in the postoperative period.

CS: Cushing's syndrome, MRI: magnetic resonance imaging, CT: computed tomography, IPSS: inferior petrosal sinus sampling.

Conflict of Interests

The authors declare that they have no conflict of interest. Statement of human and animal rights.

Data Availability

Data sharing does not applicable to this article as no datasets were generated or analyzed during the current study.

Authors' Contribution

Literature Review, Critical Review, Manuscript preparing held by all authors.

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