COVID-19 Infection in Adrenal Tuberculosis Patients with Adrenal Insufficiency Who Complicated with Adrenal Crisis

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ABSTRACT

Introduction: *Adrenal insufficiency can increase the risk of infection. Respiratory infections play a role in the greater number of mortalities in patients with primary adrenal insufficiency. Severe acute illness elevates the risk of adrenal crisis which can give lethal outcome.* ***Case illustration:*** *A 52-year-old woman came to the emergency unit due to worsening gastrointestinal symptoms for the past 3 days. She had chronic epigastric pain, general weakness, weight loss, and skin hyperpigmentation. She was suspected of primary adrenal insufficiency one year ago, but she had poor compliance. In this current admission, she was suspected to have adrenal crisis and was diagnosed with COVID-19. On the 5th day of inpatient care, her condition was worsening, and she was diagnosed with adrenal crisis, septic shock, and severe COVID-19. Her ACTH level was 78.6 pg/mL (normal range 7.4-64.3 pg/mL) and her morning cortisol level was 1.1 ug/dL (normal range 3.7-19.4). Imaging showed unilateral hypertrophy of the adrenal gland, a positive result of IGRA, and fibrotic of the lung that led to tuberculosis of the adrenal as suspected etiology.* ***Conclusion:*** *Making a diagnosis of adrenal insufficiency is challenging because of its non-specific signs and symptoms. The need for education, equipment (adequate steroid supplies), and empowerment (development of specific guidelines for PAI and COVID-19) were taught to help prevent the adrenal crisis. Further examination is needed to obtain the definitive etiology of adrenal insufficiency in this patient.*

Keywords: *adrenal crisis, primary adrenal insufficiency, COVID-19.*

INTRODUCTION

Both the adrenal crisis and severe coronavirus disease 2019 (COVID-19) can be life-threatening. An adrenal crisis occurs when the body cannot produce adequate cortisol, a hormone that regulates blood sugar levels, metabolism, and blood pressure. Adrenal crisis can be caused by multiple factors, such as infection, injury, or physical and emotional stress.[1] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, has infected millions of people worldwide.[2] The

first cases of COVID-19 were detected on March 13, 2020, in Wuhan, China. In most cases, the disease attacks the respiratory system and has varied symptoms, from mild symptoms to acute respiratory distress syndrome. In a systematic review, the prevalence of adrenal insufficiency in COVID-19 patients ranged from 3.1% to 64.3%.[3] Adrenal crisis may occur in around 1 in 12 patients with primary adrenal insufficiency (PAI) .[1] Although there are no data on the concomitant incidence of adrenal crisis and severe COVID-19, it is believed that COVID-19 can interfere with the hypothalamic-pituitary-adrenal (HPA) axis.[2] Knowledge in recognizing adrenal insufficiency and severe COVID-19 is needed to prevent adrenal crisis, which can be life-threatening. This case report describes a patient suspected of having PAI who presented with an adrenal crisis precipitated by worsening COVID-19.

CASE ILLUSTRATION

A 52-year-old woman arrived at the emergency unit of Dr. Cipto Mangunkusumo Hospital with the chief complaint of worsening vomiting three days ago. She had a history of nausea, vomitus, general weakness, 18 kg weight loss, loss of appetite, and skin hyperpigmentation in the knuckles, oral mucous membrane, and breast areola since 2021. In her past examination, she was suspected of having Addison's disease, but she refused to undergo laboratory examinations.

The patient agreed to be hospitalized because her nausea and vomiting had made oral intake difficult in the last three days. She did not have any respiratory symptoms or fever. However, she tested positive for SARS-CoV-2 when she was subjected to a polymerase chain reaction test as part of the hospital's standard of care for hospitalization. The physical examination revealed that her hemodynamic status was stable, but her blood pressure was within the lower normal limit (90/60 mmHg), and she had epigastric pain and skin hyperpigmentation at the knuckles, oral mucous membrane, and breast areola (**Figure 1**). The results of the other physical examinations were within the normal limits.

The patient's initial laboratory results were 94 mg/dL blood glucose, 128 mg/dL hyponatremia, normal potassium level (4.9 mg/dL), low estimated glomerular filtration rate (28 ml/min/1.73^m^2), and elevated d-dimer (2800 ng/mL). Her chest x-ray showed heterogeneous opacity and fibrosis in the lower lobe of her right lung, with a differential diagnosis of pneumonia or tuberculosis (TB). For COVID-19, she received remdesivir 1 × 200 mg IV on day 1, followed by a maintenance dose of 1 × 100 mg on days 2–5. She was assessed as being in adrenal crisis and planned to receive hydrocortisone 100 mg intravenously, followed by hydrocortisone 200 mg/24 h, with continuous infusion. The complete laboratory findings of the patient are presented in **Table 1**.

The patient began to complain of shortness of breath on the 5th day of her hospital treatment. She was in an altered mental state and experienced hallucinations. Her oxygen saturation was 49.6%, and her blood pressure suddenly dropped to 60/40 mmHg. She was immediately intubated, given an isotonic solution, and was started on vasopressor infusion due to her hypotension. She was then referred to the intensive care unit (ICU) for further management. Her glucose level was 39 mg/dL. The patient was diagnosed with acute adrenal crisis, septic shock, and severe COVID-19. Her continuous infusion of 200 mg/24 h hydrocortisone was titrated to 300 mg/24 h. While in the ICU, she was treated with renal replacement once because her urea level increased from 68.5 mg/dL to 104.9 mg/dL. Her blood culture showed isolated *Klebsiella pneumoniae*, and for her superimposed bacterial infection, she received meropenem (adjusted renal dose).

After being stabilized in the ICU and extubated after 162 h with a ventilator, she was moved to the high-care unit, and when her condition stabilized without a vasopressor, she was moved to the non-critical care unit. Her adrenocorticotropic hormone (ACTH) level was 78.6 pg/mL (normal range: 7.4–64.3 pg/mL), and her morning cortisol level was 1.1 ug/dL (normal range: 3.7–19.4 ug/dL). A contrast computed tomography (CT) of the adrenal gland showed hypertrophy and calcification of the right

adrenal gland, with a differential diagnosis of adrenal TB (**Figure 2**). Her interferon-gamma release assay (IGRA) showed positive results, but *Mycobacterium tuberculosis* was not detected in the sputum GeneXpert. She was discharged and scheduled for further investigation for TB in the ambulatory clinic as the cause of PAI. Hydrocortisone was continued and tapered off, based on her point-of-care testing results, to a final oral dose of 20 mg daily.

Table 1. Laboratory findings of the patient at presentation and during hospitalization.

Parameter	Day of admission	Day of worsening condition	Day of transfer to non-critical care	Day of discharge	Normal range
WBC count (10^3/mcl)	3.87	15.03	7.73	4.68	4-10
Hb (g/dL)	10.6	7.1	11.3	11.7	13-17
Platelets (10^3/mcl)	241	**97**	197	294	150-410
CRP (mg/dL)	**22.5**	**105.3**	**48.7**	**2.9**	<0.5
Procalcitonin (ng/dL)		**59.3**	**5.7**	**0.08**	<0.05
D-dimer (mcg/L)	**2800**	**6100**		**1180**	<440
Sodium (MEQ/L)	**128**	**134**	**130**	136	136-145
Potassium (MEQl/L)	4.9	**3.4**	4	3.9	3.5-5.1
Glucose (mg/dL)	94	**37**	136	100	60-140
Chloride (MEQ/L)	**96.3**	106.7	99	103	98-107
HCO3 (mmol/L)		15.4	28		21-25
Urea (mg/dL)	**68.5**	**104.9**	36.6	30	15-40
Creatinine (mg/dL)	**2**	**1.4**	0.6	0.7	0.55-1.02
eGFR (ml/min/1.73^m^2)	**28.1**	**43.2**	105	99	71-165
AST (U/L)	31	**52**	26	14	5-34
ALT (U/L)	10	27	27	19	0-55
Lactate		**10**	1.5		
TSH		1.154			
fT3		1.32			
fT4		1.1			
CD4 absolute (%)		300 (28%)			
PCR Sars Cov 2	**Positive**	**Positive**	Negative		Negative

WBC: white blood cell; Hb: hemoglobin; CRP: C-Reactive Protein; AST : aspartate aminotransferase; ALT: alanine aminotransferase; eGFR: estimated glomerular filtration rate; TSH: thyroid stimulating hormone; CD4: cluster of differentiation; PCR: polymerase chain reaction;
The bold values in Table 1 are the abnormal values.

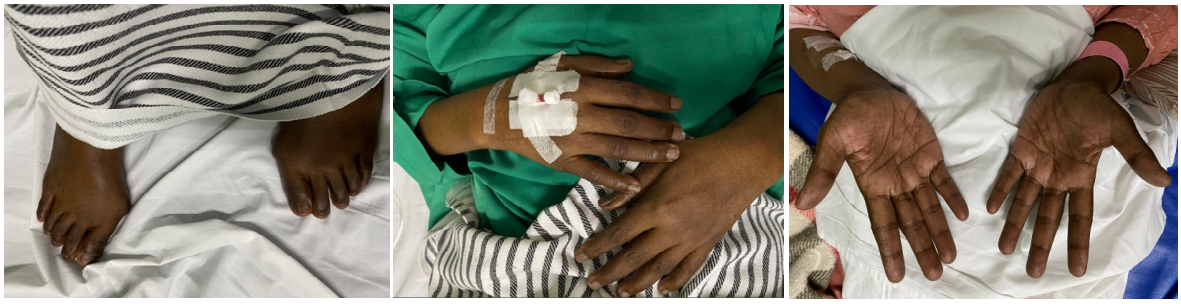

Figure 1. Hyperpigmentation in the (a) lower extremities and (b, c) upper extremities.

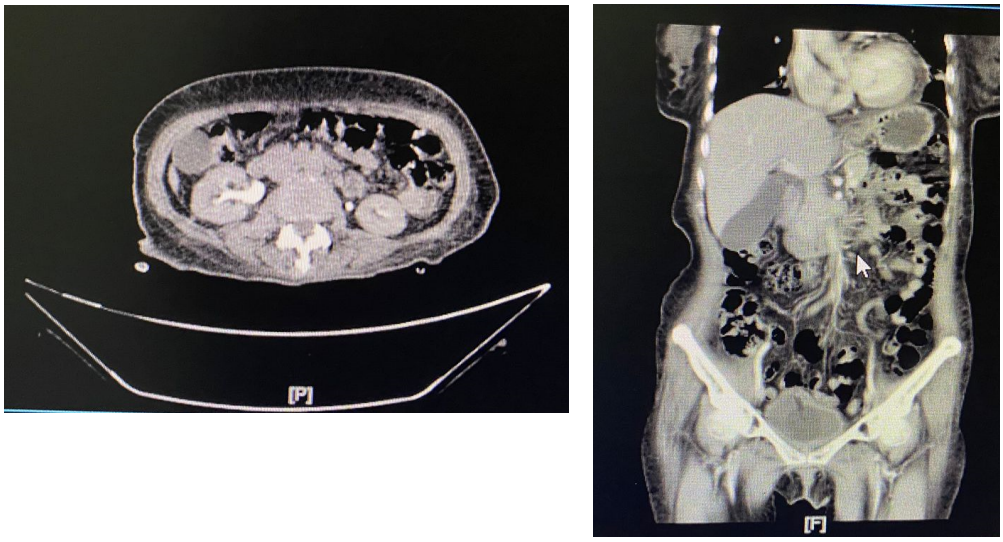

Figure 2. Computed tomography scan of the patient's abdomen showing hypertrophy and calcification of the right adrenal gland: (a) axial view and (b) coronal view.

DISCUSSION

As the prevalence of PAI is only 100–140 cases per million, it is considered a rare disease, particularly in females. The incidence of PAI is 4:1,000,000 per year in Western societies. Autoimmune disease is the most common etiology of PAI worldwide, followed by infectious diseases such as TB, candidiasis, histoplasmosis, acquired immunodeficiency syndrome, and cytomegalovirus. In developing countries, infection, particularly by *Mycobacterium tuberculosis*, is the most common etiology of PAI.[4] This is because the bacterium spreads through the bloodstream. Around 12% of patients with tuberculous adrenalitis show asymptomatic infection, and this infection will show symptoms of adrenal insufficiency when 90% of the adrenal gland has been damaged.[5]

Indonesia has the second highest prevalence of PAI in the world, accounting for more than two-thirds of the global TB cases (9.2%), according to World Health Organization data in 2021.[6] The frequency of adrenal crisis in adult patients with PAI was found to be 6.6 per 100 patient-years. The main triggers of adrenal crisis were gastrointestinal diseases (32.6%) and other infectious diseases (24.3%).[7]

There are several possible mechanisms of adrenal gland dysfunction in COVID-19. According to Suryadevara et al., cytokine storm can be one of the Patho mechanisms of COVID-19-induced adrenal insufficiency; it suppresses the HPA axis, leading to bilateral adrenal hemorrhage .[2] In 2021, Bhattarai et al. described the direct and indirect effects of COVID-19 on the renin-angiotensin-aldosterone system.[8] Direct effect blocked the release of ACTH and corticotropin-releasing hormone (CRH) on ACE-2 receptor on the hypothalamus and hypophysis. The mediator of cytokine storm, TNF-alpha, also inhibits ACTH secretion. COVID-19 is a vascular disease that makes the body prone to coagulopathy.[9] The procoagulant effect causes microthrombi of the vascularization of adrenals and influences the effectivity of cortisol secretion.[8] Adrenal insufficiency can also lead to severe infection because of inadequate innate immune response due to a lack of physiological rise of glucocorticoid secretion in acute phase response.[2] A decrease in HDL which plays a pivotal role as an essential substrate for cortisol production, can cause adrenal insufficiency because this commonly happens in severe illness. There was a term named "critical illness-related corticosteroid insufficiency" (CIRCI) used for insufficient cortisol levels for inflammation control or supplying raised metabolic demand. Frequency of CIRCI among patients with mild or severe COVID-19 was 4.4-32%.[9] SARS-COV 2 produced amino acid that mimics host ACTH and antibody production against this peptide may also be responsible for the presence of adrenal

insufficiency.[10]

She had signs and symptoms of adrenal insufficiency before admission to Dr. Cipto Mangunkusumo Hospital, which included chronic fatigue, abdominal discomfort, and hyperpigmentation. The clinician suspected an adrenal crisis at the initial assessment because of worsening symptoms although lab results still do not indicate an adrenal crisis clearly before the 5th day of admission. Routine laboratory tests revealed hyponatremia condition and low blood sugar test. The clinical practice guideline of primary adrenal insufficiency, signs, symptoms, and routine laboratory tests can help to differentiate between adrenal insufficiency and adrenal crisis. Adrenal insufficiency is suspected when the existence a general weakness, weight loss, postural dizziness, hyperpigmentation for primary only, low blood pressure, hyponatremia, and hyperkalemia. On the other hand, the adrenal crisis was suspected when the presence of severe weakness, syncope, symptoms mimicking acute abdomen (vomitus and abdominal pain), reduced consciousness, hypotension, hyponatremia, hyperkalemia, hypoglycemia, and hypercalcemia.[7]

In this patient, primary adrenal insufficiency was confirmed by laboratory tests. The patient had cortisol deficiency and increased plasma ACTH. Based on clinical practice guidelines by Bornstein 2015, primary adrenal insufficiency was diagnosed if plasma ACTH > 2-fold the upper limit of the reference and confirmed cortisol deficiency.[7] In this patient, ACTH level increased but did not reach >2-fold ULN because the patient was administered a high dose of corticosteroid previously when she had an adrenal crisis. In a guideline, steroids should not be given before blood has been drawn. However, in acute illnesses that cause life-threatening, treatment should not be delayed awaiting test results. Although the corticotropin stimulation test is a superior diagnostic rather than morning cortisol and ACTH, this test cannot be done in our hospital because of the limitations of facilities.

The adrenal crisis was precipitated by COVID-19 as an acute illness and this diagnosis was made in this patient because she had previous uncontrolled primary adrenal insufficiency and related signs and symptoms of adrenal crisis such as severe fatigue, delirium, nausea, vomiting, and hypotensive condition. Hyponatremia and lower-limit glucose were also found in our patient. Overdiagnosis of adrenal crisis was conducted at the beginning of the management of this patient because COVID-19 can be severe in sudden conditions. The worsening of COVID-19 induced more full-blown adrenal crisis manifestation in our patients. However, we have treated this patient with adrenal crisis protocol at early management.

The patient was suspected of adrenal tuberculosis because she had a positive result of IGRA, and her pulmonary examination showed fibrosis in the lung. Nomura et al stated 93% of patients with adrenal TB had a history of classical TB in the pleura or lungs. A gold standard to diagnose tuberculosis is found in *Mycobacterium tuberculosis*, Datia-Langhans cell, and necrosis caseosa area microscopically. In this patient, adrenal adenoma or malignancy should not be excluded yet because a CT scan can show similar imaging as an infection.[11] In 70% cases, hematogenous spread of infection caused involvement of bilateral adrenalitis.[12] Soedarso et al said adrenal tuberculosis is suspected if the CT scan showed bilateral enlargement but in our patient, we only found unilateral hypertrophy of the adrenal gland and calcification.[13]

Endocrinologist recently made new clinical practice guidelines about managing adrenal insufficiency varies due to clinical symptoms. Patients with mild symptoms can be given a double dose of replacement in circadian rhythm or oral hydrocortisone 20 mg per 6 hours.[7] On the other hand, in patients with critically ill or hospitalized patients, the dosage was increased and equivalent to 200 mg per day hydrocortisone IV either in a divided dose every 6 hours or as in continuous infusion.[2] This glucocorticoid replacement should be given until significant clinical improvement has occurred or weaning from mechanical ventilation.[14]

The vital roles in the management of adrenal crisis were steroid and rehydration. A rapid intravenous solution of 1000 mL NaCl 0.9% was given within the first hour and followed

by maintenance of continuous intravenous solution. Hydrocortisone, as steroid replacement, was given 100 mg intravenous immediately followed by hydrocortisone 200 mg per day as continuous infusion for 24 hour and reduce slowly to hydrocortisone 100 mg per day in the following day.[7] Management of acute conditions such as COVID-19 in our patient had been done concomitantly as well as the adrenal crisis condition to reduce metabolic demand.

Adequate management to prohibit recurrent adrenal crises in COVID-19 with primary adrenal insufficiency in this patient was enough education, sufficient equipment such as glucocorticoid supplies, and patient empowerment like updated guidelines of COVID-19 and adrenal crisis).[14]

CONCLUSION

Although COVID-19 is now an endemic disease, we should remember that acute infection may lead to adrenal decompensation and worsening adrenal insufficiency. For internists, recognizing the signs and symptoms of adrenal crisis is important in patients with suspected adrenal insufficiency because adequate treatment of Addison's disease can be fatal and can avoid unnecessary hospitalization with a recurrent adrenal crisis.[15] Giving information and education to patients is needed because adrenal insufficiency has long-term treatment and monitoring. Moreover, this patient has a history of poor compliance since 2021. Real etiology must be investigated to get definitive treatment for primary adrenal insufficiency.

COMPETING INTERESTS

There is no conflict of interest.

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CONSENT FOR PUBLICATION

Written informed consent was obtained from the patients for publication of this case report and any accompanying images for their anonymized information to be published in this article. The subject had decisional capacity to provide written consent.

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