

## Challenges in The Diagnosis and Management of Adrenal Insufficiency: A Case Report

Febri Kurniawati<sup>1</sup>, Sony Wibisono Mudjanarko<sup>1</sup>, Soebagijo Adi Soelistijo<sup>1</sup>, Agung Pranoto<sup>1</sup>

<sup>1</sup> Division of Endocrinology, Diabetes, and Metabolism, Department of Internal Medicine, Airlangga University Faculty of Medicine, Dr. Soetomo Hospital, Surabaya, Indonesia

*\*Corresponding Author:*

Febri Kurniawati, MD. Department of Internal Medicine, Faculty of Medicine Airlangga University, Dr. Soetomo Hospital, Surabaya 60132, Indonesia.

Email: febri.kurniawati-2020@fk.unair.ac.id.

### ABSTRACT

Adrenal insufficiency (AI) is a rare endocrine condition. Primary adrenocortical insufficiency, or Addison diseases reduces the production of crucial hormones, including glucocorticoids, mineralocorticoids, and adrenal androgens. Due to the lack of proper cortisol response in adrenal crisis, it can be life-threatening during times of stress, emphasizing the need for a timely diagnosis. Despite this, diagnosing and managing AI still presents significant challenges. We report the case of a middle-aged woman who presented with complaints of weight loss, abdominal pain, lethargy, hyperpigmentation of the skin and mucosa, and a history of repeated hospitalizations for nausea, vomiting, dehydration, and hypovolemia. During the patient's previous hospitalization, Addison's crisis was suspected, and methylprednisolone therapy was administered, rendering the cortisol and ACTH assays inaccurate. The patient's condition subsequently improved. The subsequent monitoring revealed low cortisol levels, but an ACTH stimulation test was unavailable. The presence of pulmonary tuberculosis was indicated by a positive chest X-ray and IFN-Gamma Release Assay (IGRA) test. With a history of repeated hospitalizations, suspected Addison's crisis, hypoglycemia, mineralocorticoid involvement (hypotension, hyponatremia), and the presence of hyperpigmentation, a clinical diagnosis of primary adrenal insufficiency was made with limited conditions and testing tools. The patient was given anti-tuberculosis treatment and the lowest dose of hydrocortisone required to control the disease without causing side effects.

**Keywords:** adrenal insufficiency, addison's disease, hypocorticism

## INTRODUCTION

Adrenal insufficiency (AI), particularly primary adrenal insufficiency, is a rare endocrine disorder that occurs when the adrenal glands cease producing enough glucocorticoids and, in some cases, mineralocorticoids and androgens.<sup>1,2</sup> AI is less common than other endocrine conditions. There is no prevalence data in Indonesia. In South Korea, the estimated prevalence of PAI was 4.17 cases per million inhabitants, which is much lower than the prevalence recorded in Western countries.<sup>3</sup> However, it is a crucial consideration in acute admissions due to significant morbidity and mortality.

Diagnosing can be challenging due to its varied presentation, and referrals to various specialties often occur before making a diagnosis.<sup>4</sup> Many patients are only diagnosed once admitted in acute primary adrenal insufficiency or Addison's crisis, which makes prompt diagnosis even more important. Crisis can also be triggered by infection sepsis, which can mask symptoms and make the diagnosis more complex.<sup>5</sup>

Several advances have been made over the past several decades in the management of AI. Still, treatment remains suboptimal even after the diagnosis, leading to poor quality of life and increased mortality.<sup>6</sup>

## CASE ILLUSTRATION

A 44-year-old Asian female presented to the outpatient department complaining of four hospitalization episodes due to general weakness, frequent vomiting, abdominal pain, dehydration, and hypotension. She was referred to a cardiologist and given some medications. Thereby, she experienced fever, inability to walk, dehydration, and hypotension. The patient was suspected of Covid infection and was referred to the Tropical Medicine division, but the result came back negative. Afterwards she experienced frequent vomiting, abdominal pain, and back pain. Then she was referred to a Gastroenterologist and underwent a gastroduodenal endoscopy. The result was nonactive, non-atrophy chronic gastritis, and

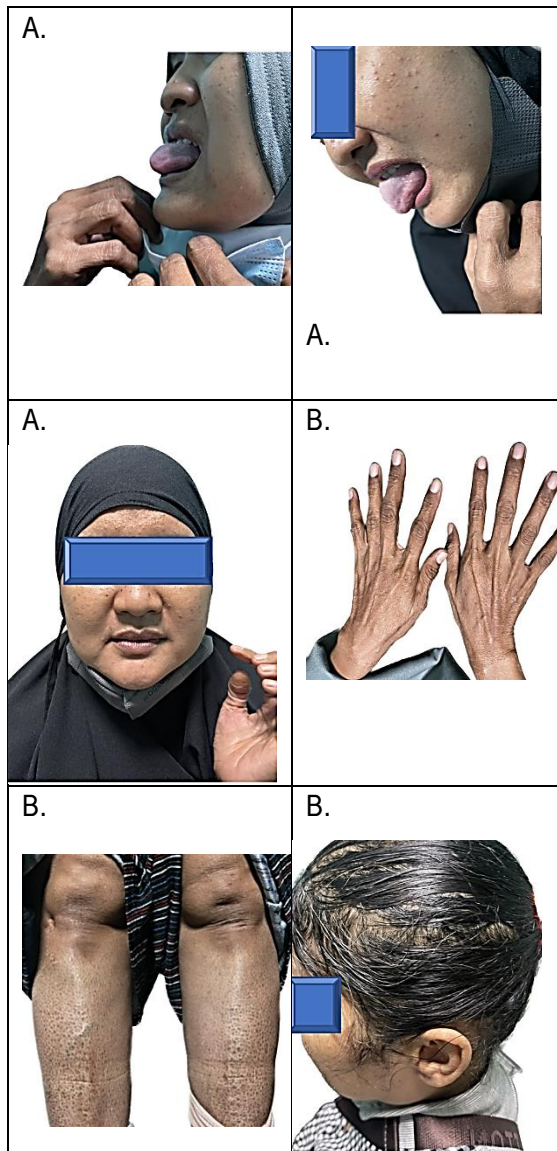
*Helicobacter pylori* were not found. Two weeks later, she underwent her third hospitalization and moved to another hospital with the same complaints.

Later, she got disorientation, breathlessness, and loss of consciousness. She was admitted to the ICU and somehow needed a pacemaker. From the examination, there were persistent hypotension, hypoglycemia, and hyponatremia. Therefore, the physician suspected her of an Addisonian Crisis. Eventually, she was given intravenous methylprednisolone, and it dramatically improved her condition. The patient was referred to the outpatient clinic at our hospital to get further analysis and treatment. At that time, she was already taking oral methylprednisolone 16 mg daily divided into two times a day since the last hospitalization.

Moreover, a history of similar complaints on and off for the past few years, wherein the local doctor treated him on the lines of gastrointestinal disorder, mainly gastritis. There was a history of weight loss (about 10 kgs in the last 12 months). On inquiry, history of skin hyperpigmentation, mainly elbows, and knees, for two years ago. Lips and oral mucosa became hyperpigmented over the last six months. Furthermore, the patient complained of frequent coughing during the past month. Her periods were coming monthly, with normal flow. But there was decreased libido. No history of tuberculosis, diabetes mellitus, thyroid disorders, liver disease, or other comorbid illnesses.

Physical examination showed a well-appearing woman who weighed 49.5 kg and was 156 cm tall, with a body mass index of 18.7. Her recumbent blood pressure was 105/70 mmHg, her heart rate was 74/min, her respiratory rate was 20/min, and her temperature was 36.5°C. No finding of pallor, lymphadenopathy, or neck swelling. Generalized hyperpigmentation on the face, palmar creases, knuckles, and elbows did not seem clear, but hyperpigmentation in oral mucosa was noted (Figure 1). The remaining physical examination findings were normal.

On examination of the abdomen system, there was no tenderness, guarding, or rigidity. The systemic examination of the respiratory, neurological, and cardiovascular systems was normal. Investigations were done for further evaluation.



**Figure 1:** (a) Hyperpigmented lips and tongue, (b) Hyperpigmentation skin, anorexic and thinly built, hair fell.

Laboratory findings from previous hospitalization, showed a hemoglobin 10.1 g/dl, a total leukocyte count  $3.37 \times 10^3/\mu\text{L}$ , differential counts and platelet level were normal. The patient was hyponatremic with serum sodium 120 meq/L (130-142 meq/L) and potassium 3.9 meq/L (3.5-5.5 meq/L), chloride 82.9 meq/L (95-

110 meq/L). Renal function tests were essentially normal. The random blood sugar was 59 mg/dL (80-110 mg/dL). The liver function tests were in the normal range. The next day after methylprednisolone intravenous was given, the condition dramatically improved; the laboratory findings showed serum sodium 136 meq/L (130-142 meq/L) and potassium 3.59 meq/L (3.5-5.5 meq/L), chloride 103.3 meq/L (95-110 meq/L). Early morning 8 am serum cortisol level was normal in this first course, 20.08  $\mu\text{g/dL}$  (normal  $>18 \mu\text{g/dL}$ ). Due to limited resources, the Cosyntropin test, plasma renin activity, and serum aldosterone level could not be examined. These average results of the cortisol level might be because the patient had already been given intravenous methylprednisolone intravenously and orally in the hospital due to the Addisonian crisis.

On the evaluation, laboratory investigations showed the hyponatremia was improved with serum sodium 137 meq/L (130-142 meq/L), potassium 4.8 meq/L (3.5-5.5 meq/L), chloride 105.0 meq/L (98-107 meq/L), the calcium 8.1 meq/L (8.5-10.5 meq/L), and magnesium 2.10 meq/dL (1.8-2.4 meq/L). Plasma ACTH level was normal 44.6 pg/ml (7.2-63.3 pg/ml).

Another lab investigation to rule out etiological factors for Addison's disease was done. Thyroid function tests showed Free T4 1.12 ng/dL (0.83-1.43) and a normal thyroid stimulating hormone TSH level 0.71  $\mu\text{U/mL}$  (0.02-132.7). HbA1C was 5.1%, serum calcium, and magnesium were 8.1 mg/dL (8.5-10.5) and 2.10 mg/dL (1.8-2.4). Autoantibodies against adrenal glands and serum levels for light chain fatty acids could not be performed. The three methods of anti-HIV examination were non-reactive, Toxoplasma IgG and IgM were non-reactive, CMV IgG was reactive 163.4 AU/mL ( $\geq 6$ ), and CMV IgM was non-reactive. We followed up and reexamined the morning cortisol serum; the result fell to  $< 1.0 \mu\text{g/dL}$  (3.7-19.4); the patient was still on methylprednisolone 16 mg/day since her last admission. The electrocardiography was normal; the sinus rhythm was 74 bpm. The summary of echocardiograph was normal left

ventricle diastolic and systolic function, ejection fraction of 59%, mild mitral regurgitation, tricuspid regurgitation, and good right ventricle contractility. The chest X-ray showed infiltration in the right and left perihilar and paracardial, suggesting pulmonary tuberculosis.

Abdominal MSCT scan and magnetic resonance imaging with contrast were utilized to conduct tests and eliminate any possibilities of adrenal abnormalities. The outcome of the tests revealed no adrenal mass detected. The test showed hepatomegaly, cholelithiasis, spondylosis thoracolumbar, bronchiectasis type varicose, and cystic on the lower of the left lung. Because adrenal tuberculosis is the most frequent cause of primary adrenal insufficiency in developing countries, we ran an IFN-Gamma Release Assay (IGRA), and the result came back positive. However, Xpert MTB-RIF assay showed MTB not detected.

With the foregoing facts, we hypothesized adrenal insufficiency which was the case of primary or Addison disease, and pulmonary TB. The patient was finally given the anti-tuberculosis drug regimen and a drug switch from methylprednisolone to hydrocortisone 20 mg in the morning and 10 mg in the afternoon. After a month, she mentioned that all her symptoms had significantly improved. She also gained 6 kilograms and noticed an improvement in hyperpigmentation. She felt her cheeks grow fat, and her hair fell out (Figure 1). Later, she was feeling well, and her weight had not increased too fast, although the morning cortisol serum was still  $<0.1 \mu\text{g/dl}$ . Her hydrocortisone dose was reduced to 10 mg in the morning and 5 mg in the afternoon; we plan to give the smallest dose to control the disease without relapsing her symptoms.

## DISCUSSION

Adrenal insufficiency (AI) is a relatively uncommon but serious condition characterized by decreased production of glucocorticoids and/or mineralocorticoids and adrenal androgens due to adrenal gland destruction or absence of stimulation. It is subdivided into primary adrenal insufficiency (PAI), also known

as Addison's disease, secondary adrenal insufficiency (SAI), and tertiary adrenal insufficiency (TAI) based on whether the disease affects the adrenal cortex, anterior pituitary gland, or hypothalamus, respectively.<sup>1,6-8</sup>

SAI and TAI are most typically caused by exogenous steroid treatment, which suppresses ACTH production. It is a pituitary-dependent decrease in ACTH secretion that leads to a decrease in glucocorticoid production. Mineralocorticoid secretion, including aldosterone, however, remains relatively normal. They are more common than primary insufficiency. Symptoms frequently appear after the steroid has been discontinued.<sup>9</sup>

Primary adrenal insufficiency, or Addison's disease, is uncommon. Annually, the incidence is 0.6 per 100,000 individuals in the population. The incidence rate of this condition varies between 4 and 11 per 100,000 individuals globally at any given time. The typical age of onset in adults is between 30 and 50 years. It is more prevalent among females.<sup>9</sup> In Western countries, the prevalence of Addison's disease ranges from 82 to 144 cases per million persons.

Autoimmune disorders account for 70% to 90% of PAI patients, with tuberculosis accounting for just 7% to 20%. However, in developing nations, adrenal TB is still the leading cause of PAI.<sup>10</sup> In South Korea, the estimated prevalence of PAI was 4.17 cases per million inhabitants, which is much lower than the prevalence recorded in Western countries. The cause of Korea's low incidence of PAI is unknown; nevertheless, it appears that some racial or regional variables may impact the disease's occurrence, given that the incidence of PAI in Korea is like that recorded in Japan (0.15 per million per year).<sup>3</sup> Several infectious processes associated with AIDS, including Cytomegalovirus, *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, *Toxoplasma gondii*, *Mycobacterium avium* intracellular, *Pneumocystis jiroveci*, and *Histoplasma capsulatum*, may cause adrenal gland destruction. Ketoconazole (an antifungal) and etomidate (a general anesthetic) are two medications that can induce AI.<sup>7</sup>

Doctors are poor at recognizing adrenal insufficiency, with two-thirds of patients presenting with symptoms of adrenal failure three or more times before receiving the correct diagnosis.<sup>2</sup> This illustrates the adage, "If you think of adrenal failure, rule it out". The diagnostic difficulty lies in that cortisol secretion has a circadian rhythm, so the sampling timing impacts the result. As a 'stress hormone,' cortisol secretion depends on the patient's health. Generally, a random serum cortisol of over 400 nmol/L at any time of the day makes adrenal insufficiency highly unlikely, while a morning serum cortisol of less than 100 nmol/L strongly suggests adrenal failure. In interpreting such results, one must consider the patient's current and prior steroid usage and conditions affecting cortisol-binding globulin, such as pregnancy or oral estrogen therapy, which can result in falsely reassuring cortisol concentrations.<sup>5</sup>

About half of the patients with Addison's disease are diagnosed only after an acute adrenal crisis. It is a medical emergency often precipitated by an infection or other forms of stress in an undiagnosed or inadequately treated patient with Addison's disease.<sup>8,11</sup> Patients present acutely unwell with severe dehydration, hypotension, or circulatory shock in this condition.<sup>12</sup>

The diagnosis of Addison's involves simple blood tests; however, in the acute setting, random cortisol can sometimes provide sufficient information. If in doubt, intravenous steroids can be given if there is a high index of suspicion without blood tests.<sup>11-13</sup>

Initially, the cortisol results in our patient were inappropriate because she had an adrenal crisis in the previous episode and had received methylprednisolone therapy without waiting for the cortisol level results. ACTH levels were also normal. However, we found that the cortisol levels were low during later follow-up.

A deficient cortisol in the presence of clinical features of Addison's disease should prompt a diagnosis, and a trial of hydrocortisone may confirm this. The key diagnostic test is a short synacthen test<sup>13,14</sup>. However, this can be

difficult in the crisis scenario since intravenous hydrocortisone should be started immediately.<sup>11,12</sup>

Unfortunately, the ACTH stimulation test is not available in our center. We were planning a re-examination of ACTH in this patient. In the case of a low or normal ACTH, a pituitary magnetic resonance imaging scan should be obtained, along with the measurement of anterior pituitary hormones.<sup>5</sup>

Hyperpigmentation of the skin and mucosae resulting from the melanocyte-stimulating activity of lipotropin, which derives from the same precursor as ACTH, is observed only in primary AI. Although hyperkalemia is observed only in primary AI, hyponatremia can also occur in secondary AI due to reduced glomerular filtration rate, increased antidiuretic hormone secretion, and possible concomitant central hypothyroidism. Patients with primary AI caused by autoimmune adrenalitis are at risk for other manifestations of autoimmune disease, such as vitiligo, Hashimoto thyroiditis, pernicious anemia, and type 1 diabetes mellitus.<sup>7</sup>

Secretion of adrenal mineralocorticoid aldosterone is regulated mainly through the renin-angiotensin system or dietary potassium. Lack of adrenal mineralocorticoid leads to increased renin release by the juxtaglomerular cells of the kidneys. ACTH does not play a significant role in the long-term regulation of mineralocorticoid secretion. However, it does stimulate aldosterone secretion acutely and transiently but to a lesser extent than angiotensin II and potassium.<sup>6</sup>

SAI is usually milder than PAI as aldosterone secretion remains intact. Hyponatremia can occur in PAI and SAI, although the underlying etiology differs in each case. In PAI, hyponatremia (and hypovolemia) is caused by aldosterone deficiency. In contrast, in SAI, hyponatremia is due to inappropriate vasopressin secretion (and water retention) due to the lack of cortisol, which leads to dilutional or hypervolemic hyponatremia.<sup>6</sup>

In this case, the Abdominal CT and MRI findings were negative, and Addison's adrenal TB as the primary infection is still questionable,

confusing the etiology of adrenal insufficiency. We found TB presentation in chest X-ray and Interferon- $\gamma$  release assays (IGRAs) positive results support pulmonary TB diagnosis.

Availability such as adrenal autoantibodies and endoscopic ultrasound for guide needle biopsy may sharpen the lack of diagnostic procedures. Some data present inaccurate percutaneous core needle biopsy of adrenal was 0–30%.<sup>15</sup> We did not use guided CT or MRI adrenal fine needle biopsy because reaching the adrenal without injuring the visceral organ was difficult. Measurement of anti-adrenal antibodies may help the diagnosis of autoimmune adrenalitis. This test is highly specific but not 100% sensitive.<sup>7</sup> Unfortunately, this test is not available in our area.

Alongside the difficulties in diagnosing this case, we faced additional challenges in its management. In the last admission, the patient was in the intensive care unit for five days and then shifted to the ward for further follow-up and management. Injections were given to correct all deranged parameters. Acute treatment included intravenous hydrocortisone, aggressive fluid resuscitation in normal saline, and inotropic support to treat hypotension.<sup>5,16</sup>

Serum cortisol level should always exceed 18  $\mu\text{g/dL}$  in severely stressed patients. Albumin and cortisol-binding globulin generally bind 90% of serum cortisol, except in severe hypoproteinemia. Free cortisol is a better AI indicator than total blood cortisol in such cases. Unfortunately, direct measurement of free serum cortisol is not widely available, and there is no formula to correct it for albumin or total protein levels. Before starting lifelong glucocorticoid medication, intensive care unit patients with serum cortisol-based AI diagnoses should be retested in the outpatient setting.<sup>7</sup>

The glucocorticoid doses commonly used during significant stress (major surgery, severe infection, myocardial infarction)—80 to 100 mg of hydrocortisone every 8 hours—are probably excessive and not based on clear evidence. Patients with intact adrenal function secrete between 75 and 150 mg/d in response to major surgery. Therefore, the maximal dose

recommended is 50 mg of hydrocortisone every 8 hours. When such a dose is administered, there is no need to prescribe fludrocortisone, even in patients with primary AI, because the high amounts of hydrocortisone will activate the mineralocorticoid receptor.<sup>6,7</sup>

Glucocorticoids are the primary therapy for all forms of AI. Although several kinds of glucocorticoids can be used, hydrocortisone (10–12.5 mg per day) is preferred because its short half-life mimics the normal cortisol circadian rhythm most closely. This dose of hydrocortisone is not associated with reduced bone mineral density. The downside is that hydrocortisone must be given twice or thrice daily.<sup>7,14</sup> The classic dose of 30 mg/d (20 mg in the morning and 10 mg in the afternoon) is probably excessive in most patients.

Medications with a long half-life, such as dexamethasone, beclomethasone, and deflazacort, can readily lead to overtreatment and should therefore be avoided. None of the currently available glucocorticoid preparations can mimic physiology exactly, and overtreatment with glucocorticoids is a common side effect. In addition, no reliable biochemical parameters exist for monitoring under or overtreatment. During glucocorticoid replacement, serum cortisol, ACTH, and 24-hour urinary-free cortisol excretion are inadequate indicators of tissue exposure to cortisol. Daily practice uses clinical judgement to determine the appropriateness of glucocorticoid dosage. Patients should be observed for weight gain, glucose intolerance, moon face, double jawline, thin skin, decreased bone mineral density, and osteoporotic fractures. The overuse of glucocorticoids can increase cardiometabolic risk and mortality.<sup>1,5</sup>

Moreover, patients with exogenous suppression of the HPA axis ('tertiary adrenal failure') may paradoxically exhibit Cushingoid symptoms due to the withdrawal of steroid medication, resulting in functional adrenal failure. For at least three weeks, steroid doses equivalent to 7.5 mg of prednisolone can cause adrenal suppression.<sup>5</sup> Due to the presence of adrenal insufficiency, the use of steroids in

tuberculosis is a definitive indication; therefore, the use of steroids must be more cautious, in addition to contemplating the adverse effects.<sup>17</sup>

## CONCLUSION

This case highlights the importance of reviewing previous admissions and considering other differential diagnoses, especially when the presenting symptom is similar. The patient had been initially referred to cardiologist and gastroenterologist, then underwent four hospitalizations, the last one with a suspicion of adrenal crisis. The more cardinal features, such as skin or mucous membrane pigmentation, may be missed, although these may not always be present. Eventually, primary AI was diagnosed almost one year after symptoms presented. Diagnosis is usually late, leading to increased morbidity and mortality. An adrenal crisis is a life-threatening emergency that requires immediate recognition and treatment.

In developing countries, adrenal tuberculosis remains the leading cause of primary adrenal insufficiency. In this case, the Abdominal CT and MRI were negative, and Addison's adrenal TB as the underlying infection is still dubious, challenging the adrenal insufficiency etiology. Chest X-ray and IGRA findings confirmed pulmonary TB. Pulmonary TB was clinically diagnosed in this patient. Anti-tuberculosis treatment was provided to the patient.

The patient was diagnosed with primary adrenal insufficiency following the occurrence of multiple Addisonian crises. The patient received hydrocortisone replacement therapy, with a dosage of 20 mg in the morning and 10 mg in the afternoon. One month later, he stated that all his symptoms had shown remarkable improvement. Our intention is to administer the minimal dosage necessary to manage the disease while preventing the reoccurrence of symptoms.

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