Primary Adrenal Insufficiency due to Tuberculosis Infection: Pitfalls in Diagnosis and Management

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ABSTRACT

Primary adrenal insufficiency (PAI) is a chronic condition in which both adrenal glands are not able to produce steroid hormones. In this article we reported a-20-year-old male with history of soft tissue tumor in thoracal region and general hyperpigmentation of skin and mucous. Laboratory findings showed hypocortisolism and adrenal computed tomography (CT) scan showed bilateral enlargement of adrenal with multiple necrotic nodular lesion and calcification, suggesting adrenal metastasis or tuberculosis infection. The interferon gamma release assay (IGRA) and histopathology review of the specimen from soft tissue tumor in thoracal region showed confirmed the diagnosis of adrenal tuberculosis. Antituberculosis drugs were started, and hydrocortisone dose were frequently adjusted. Five months after therapy the patient is clinically improved with a minimal dose of steroid.

Keywords: *Addison disease primary, adrenal insufficiency, hypocortisolism, adrenal, tuberculosis*

INTRODUCTION

Primary adrenal insufficiency (PAI) is a chronic condition in which both adrenal glands are not able to produce steroid hormones. Back in 1855, Thomas Addison described six cases of bilateral adrenal destruction due to tuberculosis infection. As an anti-tuberculosis drug was introduced, the incidence of adrenal tuberculosis worldwide rapidly decreased. Nowadays in the western world, the most common cause of primary adrenal insufficiency is autoimmune disease, yet in many developing countries bilateral adrenal infection including tuberculosis, histoplasmosis, and human immunodeficiency virus is still common. Left undiagnosed and untreated, this will lead to fatal condition of adrenal crisis.[1,2]

Commonly, adrenal tuberculosis is secondary to tuberculosis infection elsewhere and affects both adrenals. It spreads through hematogenous route to adrenal glands. Symptoms of adrenal tuberculosis are not specific and slowly developed due to the chronic nature of *M. tuberculosis* bacteria. To give full-blown symptoms of adrenal insufficiency, both adrenal glands must have been destroyed up to 90%.[3] General symptoms of tuberculosis such as anorexia, malaise, fever are not specific and often overlooked by most patients. Both computed tomography scan (CT-scan) and magnetic resonance imaging (MRI) cannot precisely differentiate between adrenal tuberculosis and other bilateral adrenal pathologies such as adrenal malignancy, metastasis, hemorrhage, or fungal infections.

The commonly used of fluorodeoxyglucose positron emission tomography (FDG-PET) scan to diagnose malignancy can also lead to falsely positive results because any underlying chronic inflammation will also be shown as hot spots in FDG-PET scan indicating possible malignancy.[4] Definitive histology diagnosis through laparoscopic biopsy is quite invasive, expensive, not widely available, and easily turned down by many patients. In this paper, we report a diagnostic difficulties and management of primary adrenal insufficiency in a-young-male patient, highlighting the need of aggressive trait of suspiciousness from clinicians in the setting of limited resources.

CASE ILLUSTRATION

A-20-year-old male patient was referred to Endocrinology Clinic of Cipto Mangun kusumo Hospital with a two-year history of general hyperpigmentation of the skin. The hyperpigmentation started from fingers, toes, gum, and continued spreading to whole skin. Fever, malaise, and anorexia were absent although patients complained about not gaining weight over the years. Other symptoms of low energy level, worsening fatigue, salt craving, loss of libido, and erectile dysfunction were also absent. The patient denied having contact with tuberculosis patients or any people with chronic cough. The patient also complained of having soft tissue tumor in his chest. Previous illness and family history were unsignificant. The patient was not on any medication or substances. At that point, the patient consulted a skin specialist and was given systemic and topical treatment for the hyperpigmentation yet did not show any improvement. As for the tumor in the chest, the patient had it removed, and the histopathology showed non-specific chronic inflammation.

One year later, the patient complained of having anorexia, unintended weight loss up to 10 kg, and easily feeling tired during exercise. Patient consulted to private hospital and was suspected to have hormonal problems. The patient was then referred to Cipto Mangun kusumo Hospital. On his first visit to our hospital, physical examination showed general hyperpigmentation of skin and gum. Vital signs and other organ examinations were within normal limit. Considering history and physical findings, we were suspicious that the patient had low level of cortisol and began the investigation for adrenal insufficiency.

Initial laboratory findings showed very low level of morning cortisol (1.1 ug/dL) and low blood sugar level (2-hour-post meal 95 mg/dL). Sodium, potassium, and calcium levels were still within normal limit. To confirm the diagnosis and

determine the cause of hyporcortisolism, cosyntropin stimulation test (CST) along with basal adrenocorticotropic hormone (ACTH) level measurement were scheduled.

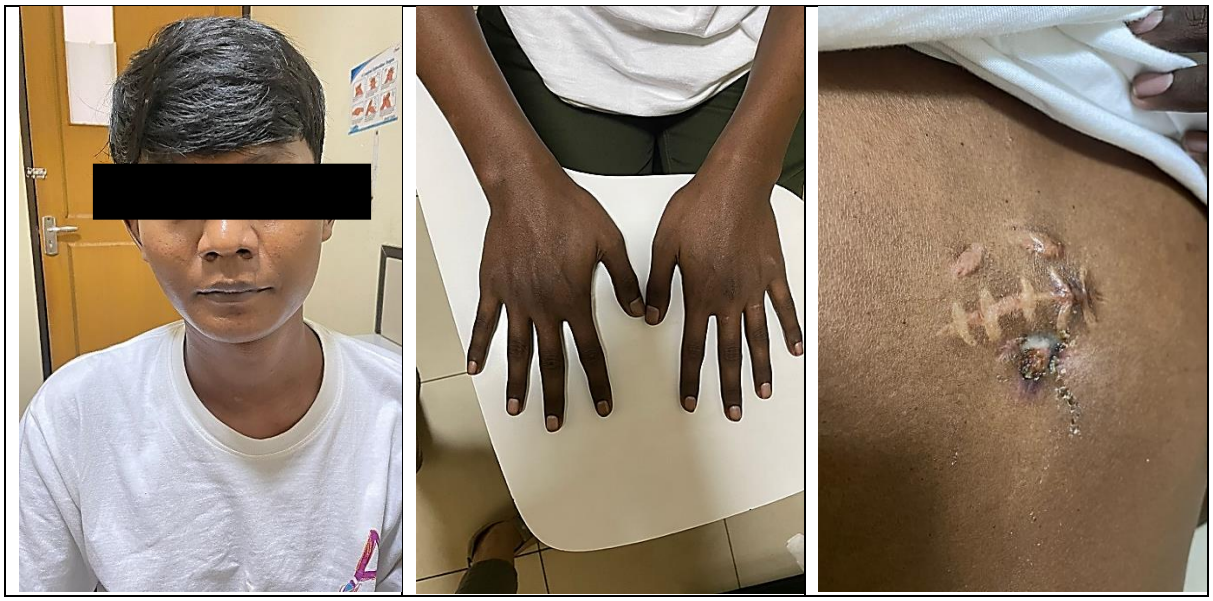

Figure 1. General hyperpigmentation and scar of post-removal soft tissue tumor in thoracal region.

During that waiting period, the patient experienced worsening fatigue with blurry vision and was rushed to the emergency room. At admission, the patient was found lethargic and hypotensive (blood pressure 90/60 mm/Hg). Laboratory findings showed severe hyponatremia (111 mEq/L), hypoglycemia (70 mg/dL), and hyperkalemia (5 mEq/L). The patient was assessed with adrenal crisis and started given intravenous hydrocortisone. The initial dose of hydrocortisone given was 100 mg twice daily for three days and tapered off accordingly. We also obtained measured ACTH level and the result was within normal limit (14 pg/mL). However, this result was neither reliable nor valid as it was taken after the patient had been given intravenous hydrocortisone for 3 days. After being hospitalized for seven days, the patient was clinically improved and discharged with oral hydrocortisone. The total hydrocortisone dose given during hospitalization was 900 mg.

Table 1. Laboratory Findings

	Reference	Initial (April 4th)	Emergency room (June 27th)	Hospital ward (June 30th)
Cortisol	3.7 - 19.4 ug/dL	1.1		128*
ACTH	6 - 40 pg/mL			14*
TSHs	0.35 - 4.94 µIU/mL	3.392		
Prolactin	3.46 -19.4 ng/mL	31.2		
Potassium	3.5 - 5.1 mEq/L	3.5	5	
Natrium	136 - 145 mEq/L	135	111	
Fasting blood glucose	<100 mg/dL	85		
Post-prandial glucose	<200 mg/dL	95		

*Sample was taken while patient on intravenous hydrocortisone

On his follow-up visit at endocrinology clinic, the investigation of adrenal insufficiency was resumed aiming to find the root of the condition while continuing oral hydrocortisone. The abdominal CT-scan showed bilateral enlargement of adrenal with multiple necrotic nodular lesion and calcification, suggesting adrenal metastasis or adrenal tuberculosis. Laparoscopic biopsy of adrenal was considered, but the patient and his family preferred any non-invasive diagnostic method and put surgery as the last option. Evaluation of several tumor markers such as carcinoembryonic antigen (CEA), alpha fetoprotein (AFP), lactate dehydrogenase (LDH), and cyfra-21 came back negative. The viral marker for chronic hepatitis infection and antibody against HIV infection also showed negative results. The Interferon Gamma Release Assays (IGRA) test was positive suggesting tuberculosis infection. This finding was strengthened by the re-expertise result of histopathology specimen from soft tissue tumor in thoracal region that showed granuloma, Datia Langhans cell, and caseous necrosis area compatible with chronic tuberculosis infection.

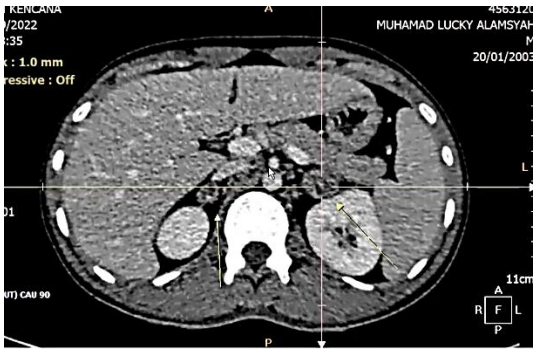

Figure 2. Adrenal contrast CT-scan showing bilateral adrenal enlargement with calcification and necrosis.

Following these findings, the patient was started with category 1 anti-tuberculosis drugs (ATD) and adjusted dose of oral hydrocortisone was continued accordingly. There were not either significant side effects of ATD or drug interaction between ATD and hydrocortisone. Three months after initiation of ATD and the oral hydrocortisone dose was tapered to only 10 mg once daily. Evaluation of morning plasma cortisol level was obtained by previously putting off hydrocortisone one day before the examination and the result of morning plasma cortisol level was 8.2 ug/dL. Even though the result was quite promising, the ultimate target of treatment for this patient is to have a- working-hypophyseal-adrenal axis. To evaluate this axis, a short synacten test will be the most appropriate approach. So, the patient was scheduled to have the test when the daily hydrocortisone dose used is close to physiologic dose of endogenous cortisol secretion and clinically stable. Anatomic improvement of adrenal gland will also be evaluated using abdominal CT scan and was scheduled after completion of ATD.

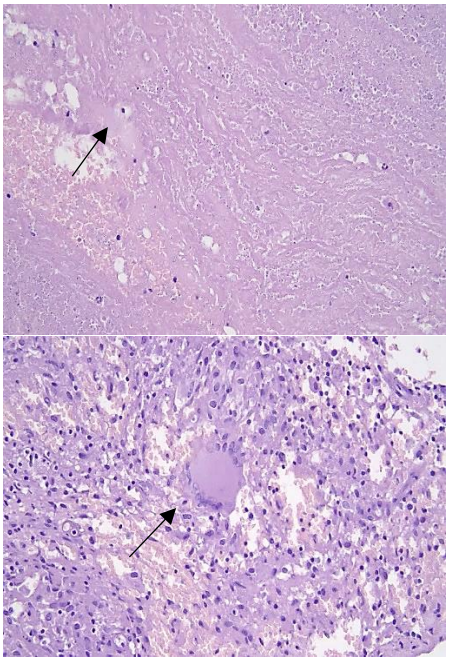

Figure 3. Histopathology finding of thoracal soft tissue tumor showing Datia Langhan's cell and caseous necrosis.

DISCUSSION

Primary adrenal insufficiency is a condition when both adrenal glands were destroyed poor enough to not be able to produce enough cortisol and other adrenal hormones. The destruction of the glands can be caused by autoimmunity, malignancy, surgery of trauma, hemorrhage and thrombosis, infiltration, or chronic infection. Table 2 showed different causes of primary adrenal insufficiency.[5]

Different from western world where autoimmune diseases are the most common cause of PAI, in many developing countries including Indonesia, chronic infection such as histoplasmosis, histiocytosis, tuberculosis, and HIV are the most frequent culprit.[1,2]

Table 2. Causes of primary adrenal insufficiency[5]

Causes	Prevalence (%)
Autoimmune adrenalitis	70-90
• Isolated adrenal insufficiency	
• PAS type I, II	
Infectious adrenalitis	20
• Tuberculosis	
• HIV infection	
• Fungal infection	
• Syphilis	
Metastatic cancer (lung, breast, stomach, colon, lymphoma)	10
Adrenal hemorrhage/infarction	-
Drugs (ketoconazole, fluconazole, rifampin, phenytoin, barbiturate)	-
Others	
• ALD/AMN	
• Congenital adrenal hypoplasia	
• Familial glucocorticoid deficiency/resistance	

***PAS:** polyglandular autoimmune syndrome, **ALD/AMN:** adrenoleukodystrophy/Adreno myeloneuropathy*

Symptoms of adrenal insufficiency include hyperpigmentation of skin and mucous, low energy level, salt craving, loss of libido, erectile dysfunction, and fatigue. In PAI, these symptoms are not always clearly shown until after 90% of both adrenal glands are destroyed. The patient presented in this case was first complained of chronic general hyperpigmentation of skin and gum that were not improved despite medication from skin specialist. Other symptoms of adrenal hormone deficiency were not present until after some years later. Hyperpigmentation in PAI is due to increased production of α-melanocyte-stimulating-hormone (αMSH). Both ACTH and αMSH are made from the same pro-hormone called peptide pro-opiomelanocortin (POMC) in which its production is triggered by hypocortisolism.

Table 3. Sign and symptoms of adrenal tuberculosis[3]

Signs and symptoms	Prevalence (%)
Anorexia	75-100
Fever	72-94
Weakness	72-100
Fatigue	70-100
Hyperpigmentation	65-94
Gastrointestinal symptoms (nausea, vomiting, abdominal pain, constipation, diarrhoea)	58-92
Hypotension (systolic blood pressure <110 mmHg)	50-90
Salt cravings	5-16
Giddiness	4-12
Vitiligo	10-120
Muscle or joint paint	5-10

Proper diagnosis of adrenal insufficiency is obtained through cosyntropin stimulation test (CST). Hypocortisolism is confirmed when cortisol level, either at 30 minutes or 60 minutes after 250 ug cosyntropin injection, is below 18 - 20 ug/dL. High level of baseline ACTH confirms the diagnosis of PAI while low level of ACTH suggests either secondary or tertiary adrenal insufficiency. Some reviews showed that morning cortisol level below 3 ug/dL is a strong predictor for adrenal insufficiency, yet CST is still needed.[7,8] The patient had initial morning cortisol level as low as 1.1 ug/dL and was prepared to have CST. At that time, the physician was not yet starting hormone replacement because other laboratory findings were still within normal limit and the patient was clinically stable. Adrenal crisis took place when certain trigger happened in a restricted cortisol availability condition. In this patient, vigorous physical activity was thought to be the trigger of the crisis and intravenous hydrocortisone was started immediately in the emergency department. Whenever signs and symptoms of adrenal crisis were found in suspected PAI patients, hormone replacement must never be delayed for diagnosis confirmation. Keeping one serum sample before administering steroid is a crucial step to ensure the validity of cortisol and ACTH level results.[9]

Determining the cause of PAI can be tricky as there are several differential diagnoses. Most endocrinology guidelines recommend detecting 21-OH-antibody in all adult patients suspected with PAI and proceed with abdominal CT if the antibody is not detected.[6] What must not be forgotten is that chronic infection such as tuberculosis is epidemiologically common in developing country and reasonable to be first considered as the cause of PAI. Adrenal tuberculosis is almost always secondary to primary tuberculosis elsewhere. Consequently, the effort to find the primary tuberculosis, either active or latent infection, in any other organ should be done vigilantly.[1,2] There were no specific imaging finding of adrenal tuberculosis. Bilateral enlargement, calcification, and necrosis can be suggestive but not conclusive. Laboratory findings may show elevated erythrocyte sedimentation rate (ESR), lymphocytosis, positive IGRA and purified protein derivative (PPD) test. Histopathology finding from laparoscopic surgery can confirm the diagnosis.[1,3] In this case report, test detection for 21-OH antibody was not performed due to resources limitation. Adrenal CT-scan showed atypical findings, as expected. However, positive results of IGRA and classic histopathology findings from thoracal soft tissue tumor led to confirmation of previous tuberculosis infection.

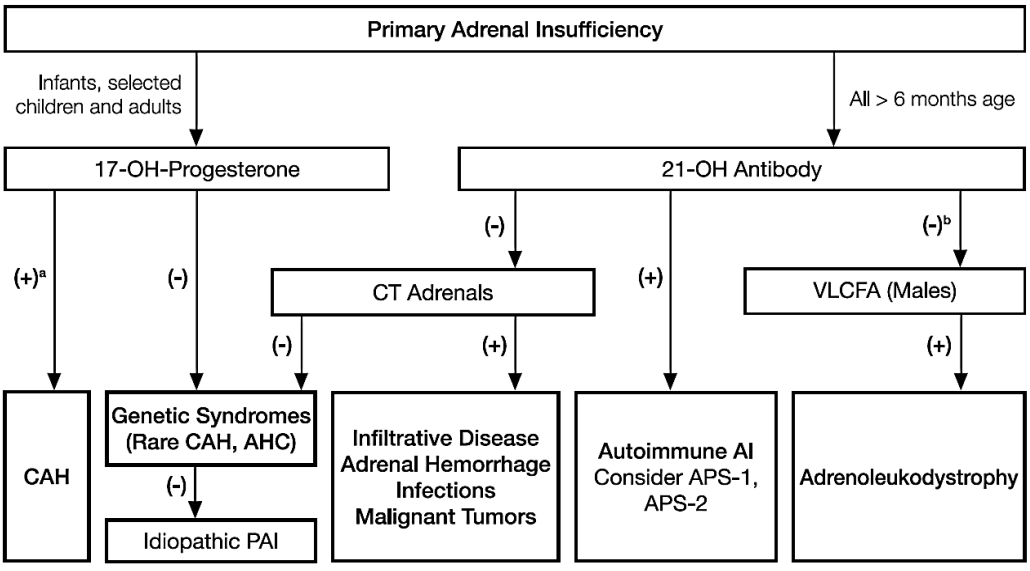

Figure 4. Diagnostic algorithm of primary adrenal insufficiency[7]

With chronic infection and overt adrenal insufficiency, antituberculosis drugs do not always successfully restore hormonal function.[10] Younger age, shorter disease duration, and less severe clinical symptoms might result in better outcome.[11] Not all those criteria were fit with this patient, so there is possibility that the adrenal function might not be fully recovered, and long-term hormone replacement will be needed. To encourage better chance in adrenal function reversibility, earlier initiation of ATD can result in better recovery of adrenal function.

However, one must always be aware of the effect of rifampicin on glucocorticoid metabolism. Rifampicin is a potent inducer of hepatic enzyme and failing to adjust the dose of glucocorticoid replacement therapy while initiating ATD may result in baneful adrenal crisis.[12]

CONCLUSION

Tuberculosis infection should be considered in young patients with overt clinical signs and symptoms of PAI. High index of suspiciousness is necessary to confirm primary tuberculosis infection elsewhere. Anti-tuberculosis drug along Glucocorticoid replacement is the mainstay treatment and- might give a better outcome when given at earliest time of diagnosis.

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