Primary Hyperaldosteronism Due to Adrenocortical Adenoma: a Case Report

Tjokorda G.D. Pemayun[1], Ridho Naibaho[1], Maretina W. Wiyati[1], Ardy Santosa[2], Siti Amarwati[3]

[1] Department of Internal Medicine, Faculty of Medicine Diponegoro University - Kariadi Hospital, Semarang, Indonesia.
[2] Department of Surgery, Faculty of Medicine, Diponegoro University - Kariadi Hospital, Semarang, Indonesia.
[3] Department of Pathology Anatomy, Faculty of Medicine, Diponegoro University - Kariadi Hospital, Semarang, Indonesia.

Corresponding Author:
Tjokorda Gde Dalem Pemayun, MD., PhD. Division of Endocrinology, Metabolism and Diabetes, Department of Internal Medicine, Faculty of Medicine, University of Diponegoro - Kariadi Hospital. Jl. Dr. Soetomo no. 16, Semarang 50244, Indonesia. email: tjokdalem_smg@yahoo.com.

ABSTRAK

Hiperaldosteronisme primer merupakan kelainan adrenal dimana sekresi hormon aldosteron terjadi secara otonom. Kami melaporkan sebuah kasus seorang wanita suku Jawa berusia33 tahun yang datang karena hipertensi yang sulit dikendalikan, kelemahan, kram otot, dan sesak nafas saat aktivitas yang memberat dalam kurun waktu 6 tahun belakangan ini. Riwayat hipertensi sudah berlangsung sejak usia 20 tahun. Kadar kalium serum selalu rendah dengan kaliuresis yang berlebihan. Dari analisa gas darah didapatkan metabolik alkalosis. Sonografi abdomen memperlihatkan arsitektur hipoekoik pada daerah suprarenal dekstra; pada CT scan abdomen terdapat tumor adrenal dekstra berukuran 4 cm. Evaluasi endokrin menunjukkan konsentrasi aldosteron plasma yang meningkat, aktivitas renin tersupresi dengan rasio aldosteron/renin 112 dan mengkonfirmasi hiperaldosteronisme primer. Pasien tersebut kemudian menjalani adrenalektomi unilateral. Laporan histopatologi dari tumor adrenal sesuai dengan adenoma korteks adrenal benigna. Pasien kemudian dapat rawat jalan dengan tekanan darah yang lebih terkontrol dengan kalium serum yang normal. Saat ini tidak ada keluhan lagi.

Kata kunci: *hipertensi, hipokalemia, hiperaldosteronisme, adrenalektomi, adenoma korteks adrenal.*

ABSTRACT

Primary hyperaldosteronism is an adrenal abnormality in which there is some degree of autonomy of aldosterone secretion. We report a case of thirty three years old Javanese female presented with uncontrolled hypertension, muscular weakness, cramps and progressing shortness of breath during working for 6 years. She had history of hypertension since age 20. Her serum potassium level was always low that associated with inappropriate kaliuresis. Blood gas analysis revealed metabolic alkalosis. Sonography of the adrenal gland showed right hipoechoic architecture; CT scan of the abdomen confirmed an right adrenal tumor measured 4 cm in its greatest dimension. Endocrine evaluation revealed high plasma aldosterone concentration, suppressed plasma renin activity, aldosterone/renin ratio of 112 and confirmed the diagnosis of primary aldosteronism. She underwent unilateral adrenalectomy. Histopathological report from excised adrenal tumor were compatible to benign adrenocortical adenoma. The patient discharge home with well controlled blood pressure and normokalemia. No clinical symptoms was reported in follow-up.

Keywords: *hypertension, hypokalemia, hyperaldosteronism, adrenalectactomy, adrenocortical adenoma.*

INTRODUCTION

Primary hyperaldosteronism (PA) is an adrenal abnormality in which there is some degree of autonomy of aldosterone secretion above that required for electrolyte homeostasis, independently of the renin-angiotensin system.[1] As first described by dr. Conn in 1954, PA is characterized by arterial hypertension, hypokalemia, excessive urinary excretion of potassium and metabolic alkalosis, associated with increased a sodium-retaining hormone which was subsequently known to be aldosterone. That original report specifically refers to aldosterone-producing adenoma (APA)[2] but currently it is realized that PA could derived from six different entity in adrenal gland.[1,3] Most case (~ 90%) are belongs to one of two major subtypes: unilateral adenoma (APA) or bilateral idiopathic adrenal hyperplasia (IHA) and the rest (<10%) are classified into less common subtypes such as adrenocortical carcinoma and several familial form. It is the commonest cause of potentially curable secondary hypertension when diagnosed in both florid and less florid form.[3]

In Jakarta, there is a report about six series of Conn syndrome reported by Siregar,[4] thus we herein described an additional case report from Dr. Kariadi hospital Semarang. Diagnosis of aldosteronism was confirmed by clinical features, hormonal evaluation, imaging study, operation section and pathology examination. The aim of this report is to report our first experience managing such case from a clinicopathological conference.

CASE ILLUSTRATION

Mrs. DL is a 33 year old Javanese female, admitted for rest and night-time worsening dyspneu and palpitations. Six years earlier, she was admitted with the same symptoms but reported progressing severity during the past 2 weeks. She also complained muscular weakness and cramps. The patient denied any recent weight gain, extremity oedema, headaches, chest pain, fever, or any constitutional symptoms.

The patient reported the following personal antecedents: arterial hypertension for a possible 13 years' duration (hypertension onset at 20 years old) and already prescribed by captopril 25 mg tid, amlodipin 5 mg tid, bisoprolol 5 mg, and clonidine 0.15 mg bid at presentation. She was also diagnosed having secundum atrial septal defect by echocardiography. In 2007, the patient was admitted for obstetrical reason but it was the first time we record her hypokalemia and later put her on potassium tablets (24 mMol/day) at home. However, no satisfactory blood pressure control and potassium serum concentration was achieved during routine out-patient visit and the patient began to complain in intense weakness characterized by incapacity to perform her normal activities, such as sweeping the floor and washing the clothes. She sought for medical care again in 2008 at Dr. Kariadi hospital when disabling generalized muscular weakness and intense cramps occurs. In regard to familial antecedents, the patient reported no other family members except her mother has hypertension.

On physical examination, she was fully alert. Her height was 160 cm and she weighed 48 kg, with body mass index of 18.75 kg/m^2. Her blood pressure in the supine position (right upper limb) was 170/115 mmHg; her pulse rate was 88 bpm. The fundi showed a grade 2 hypertension retinopathy. Cardiac examination denotes LV enlargement, fixed and split P2 and IVth degree pansystolic murmur at the upper left border of the sternum on auscultation which consistent with atrial septal defect. The abdominal examination showed no organomegaly or any palpable mass. No striae or abdominal bruits on examination. Her lower limbs showed symmetric palpable pulses, no edema, but diminished extremity motoric streghth.

Laboratory and Radiologic Findings

Routine laboratory test, which consisted of a complete blood count, blood glucose, ureum and creatinine were normal (**Table 1**) except for hypokalemia (2.2 mMol/L) which is refractory though repeated potassium correction via intravenous line (ranged from 1.9 to 2.6 mMol/L). While on a normal sodium diet, urinary potassium excretion was inappropriately high at 33 mMol/L/24 hour (serum K+ was 2.1 mMol/L at the time) and sodium excretion was 78 mMol/L/24 hour. The following studies were done to confirm the clinical impression of primary hyperaldosteronism: Plasma renin

Table 1. Laboratory data and blood gas analysis

Variables	Results	Normal value
Laboratory examination		
Hemoglobin, g/dL	12.0	12-15
Hematocrit, %	36.6	35-37
Leukocyte, /mm^3	7.200	5.000-10.000
Random blood glucose, mg/dL	104	<200
Creatinine, mg/dL	0.98	0.5-1.5
Sodium, mMol/L	140	135-145
Potassium, mMol/L	2.2	3.5-5.0
Calcium, mMol/L	2.1	2.1-2.5
Magnesium, mMol/L	0.87	0.74-0.99
Urinary potassium excretion, mMol/24 hour	33	<30
Blood gas analysis		
pH	7.57	7.35-7.45
FiO_2, %	32	
PO_2, mmHg	112	83-108
PCO_2, mmHg	33	35-45
HCO_3, mMol/L	34.1	18-23
Excess base	+11.6	±2.5
O_2 saturation, %	99	95-100
Hormonal examination		
Plasma aldosterone, ng/dL (supine)	56	<15
Plasma renin activity (PRA), ng/mL/hour	<0.5	0.7-3.3
Aldosterone/PRA ratio	112	<30

activity (PRA) was <0.5 ng/mL/hour and plasma aldosteron concentration (PAC) was 56 ng/dL; postural stress test was not performed. The aldosteron/renin ratio (ARR) being 112 ng/dL per ng/mL/hour. The arterial blood gas was as follows: pH = 7.57; PO2 = 112 mmHg with 32% FiO2; PCO2 = 36 mmHg; HCO3 = 33 mMol/L; BE = + 11.6; O2 saturation = 99%; AaDO2 = 71.

Chest X-ray showed pancardiomegaly (**Figure 1**). The electrocardiogram showed sinus rhythm with a ventricular rate of 82 x/minutes. There was a left axis deviation, left ventricular hypertrophy with pressure overloading strain, and an alteration in ventricular repolarization due to marked hypokalemia (unspecific ST-T segment depression, fusion of flattened T wave with prominent U wave; K+ serum was 2.1 mMol/L). The echocardiogram showed left ventricular hypertrophy (IVS=19 mm; LVPWd= 18 mm;

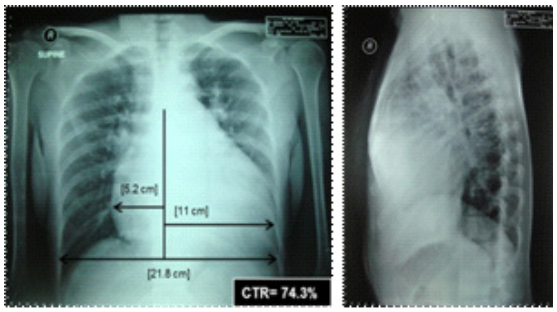

Figure 1. Chest radiography before surgery showing enlarged cardiac sillhoutte, cardiothoracic ratio >55%.

LV mass=518.72 g; LV mass index=357.7 g/m^2) and interatrial septum gap diameters 2.4 x 2.7 cm with left to right shunt. Four chamber dilatation and global ventricular hypokinetic, LV systolic dysfunction with a significant decreased global LV performance (LVEF=23%).

By 2008, an ultrasound revealed a 3.4 x 2.3 x 2.1 cm supra-adrenal mass that was confirmed with computed tomography (CT) scan studies. At that point, surgery was advised. However, the patient refused our offer and pharmacological treatment was chosen by prescribing spironolactone 50 mg bid. In this current admission, CT image was re-ordered and showed a relatively similar features of the mass compared to six years earlier. (**Figure 2a and 2b**). Unenhanced CT scan shows a hypodense nodular lesion in the right adrenal gland, round in shape of homogenous density and well defined in outlined. This nodule enhance only minimally after contrast medium injection with low attenuation values of +5 Hounsfield Unit (HU), portovenous phase has an attenuation of +27 HU; no delayed venous phase is available and therefore the absolute washout cannot be estimated.

Diagnosis of aldosteronism and right adrenal mass was made from clinical and radiological findings. Other medical diagnosis including hypertensive heart disease, LV systolic dysfunction (LVEF=23%), left to right shunt-secundum atrial septal defect with moderate pulmonary hypertension (WHO functional class II) and simple left renal cyst. At this point, we prescribed Ramipril 5 mg qd, Amlodipin 5 mg qd, Bisoprolol 5 mg qd, and Spironolactone 100 mg bid with titrated doses and arranged an

elective unilateral adrenalectomy. Spironolactone dosed were maximalized up to 200 mg bid (total 400 mg/day) for pre-operative preparation to control blood pressure and hypokalemia. The serum potassium level was sought to be maintained above 3 mMol/L by supplementation and intravenous replacement. After sufficient preparation, the patient was submitted to exploration of the right adrenal mass via a posterior approach. An adrenal tumor measuring 4 cm in greatest dimension in size was resected (**Figure 2c**). The patient made an uncomplicated recovery post-operatively.

The resected adrenal gland was a single, well-delimitated and yelowish nodule weighed 39 g and measured 4.1 x 2.5 x 1.5 cm (**Figure 2d**). Histologically, the adrenal gland showed an encapsulated epithelial neoplasia with cell of abundant clear cytoplasm and round, uniforming-appearing nuclei. Vasculature and sinusoid structure was abundant; the picture (**Figure 3a and 3b**) are shown below and the diagnosis of benign adrenal cortical adenoma was favored.

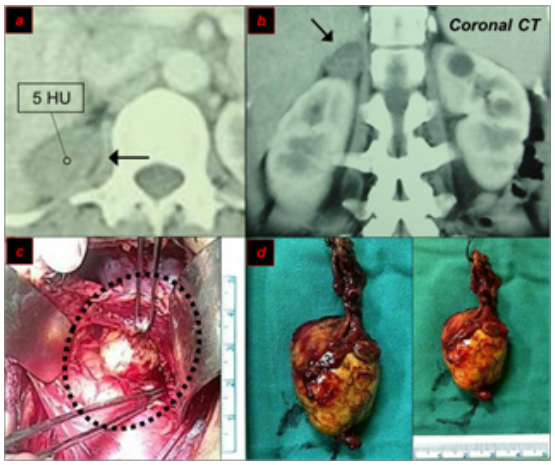

Figure 2. Adrenal tumor visualization. Pre-operatively: (a) Axial and (b) coronal CT section of the abdomen showing a solitary tumor in the right adrenal topography (black arrows). (c) Intra-operative view and (d) Gross appearance of the specimen showing a 4 x 2.5 cm exophytic adrenal mass excised from right suprarenal area. The tumor is sharply circumscribed and is non-necrotic. The yellow color was thought results from the abundant lipid within tumor.

Approximately 3 days after surgery, the patient remains clinically stable and has adequate control over her blood pressure level using Ramipril 5 mg qd. Subsequently, her serum

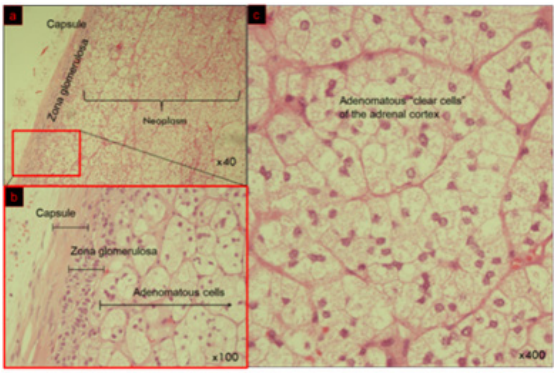

Figure 3. Adenocortical adenoma comprising of lipid-laden cells arranged in an alveolar pattern. Hematoxyline and eosin stain, (a) magnification x40 and (b) x100. (c) Tumor cells had clear cytoplasma, round and uniform nuclei, which favored adrenocortical adenoma (x400).

potassium concentration was normalized without any supplementation. The patients was discharge home then and showed stable biochemical findings based on outpatient control.

DISCUSSION

The patient presented here fulfilled all criteria for PA, i.e. hypertension, hypokalemia, and metabolic alkalosis, together with elevated aldosterone and suppressed renin level. Hypertension is caused by excessive sodium retention and body fluid expansion mediated by the aldosteronism. Hypokalemia results from the urinary loss of potassium, because it is exchange for sodium in the distal renal tubule under the influence of aldosterone. Patients also exhibit various neuromuscular symptoms such as muscular weakness, cramps, parasthesia, and muscle paralysis related to severe hypokalemia. Volume expansion and sodium retention cause inhibition of renal release of renin, which lead to low PRA. This disease, usually has its origin in a demonstrable adrenocortical tumor that secretes excessive amounts of aldosterone, a salt-retaining hormone.[1,2] As a starting point for this discussion, such a case of right adrenal tumor and hyperaldosteronism is presented. We proposed a working rules for diagnostic categorization of the tumor are defined by considering clinical and endocrinology status.

A consensus held by the endocrine society indicates that testing should be performed in patients with Joint National Commission stage

2 (systolic/diastolic blood pressure >160/90 mmHg), drug resistant hypertension, hypertension with spontateous hypokalemia, hypertension with adrenal tumor and hypertension at young age (<40 years old) in which are compatible with the patient status.[5] When hypokalemia is due to inappropriate kaliuresis (urinary losses >25 to 30 mMol/day), the yield of finding potentially primary hyperaldosteronism can be 75%.[6] Accordingly, this patient should be evaluated further to detect the presence of eminently treatable aldosterone-producing adrenocortical tumor. For that purposes, PAC and PRA was regarded as the case finding tests. The results are: high PAC (56 ng/dL) in conjuction with suppressed plasma renin activity. A PAC/PRA ratio of >100 and PAC of >15 ng/dL already meets the criteria of hyperaldosteronism, at least demonstrated an autonomous (not dependent on renin-angiotensin stimulation) aldosterone secretion.[5,6]

Detailed radiological needs to be performed to provide greater diagnostic certainty and to lateralized the disease. CT and MRI scanning are used by most institutions as a first line investigation to accurately detect adrenal lesions on anatomical basis. From abdominal CT scan, we can see a right adrenal tumor. The basic philosophy when we faced with a tumor is to discriminate first whether the neoplasma is due to benign (adenoma) or malignant (carcinoma) origin. Adrenal carcinoma usually presents with pronounced constitutional symptoms (fever, weight loss, night sweats), abdominal pain, flank mass (>6 cm in diameter) and actually was a negative finding based of our patient history, physical examination and imaging study. In addition, clinical diagnosis of benign adenoma is more likely if the adrenal tumor are associated with several phenotypes includes more severe high blood pressure, more pronounced hypokalemia (<3 mMol/L), higher level of aldosterone (>25 ng/dL) and younger age (<50 years).[7] In our case, the visualized adrenal tumor which is oval in shape, well circumscribed contour with contrast attenuation < +10 HU in an unenhanced CT is highly suggestive of adrenal adenoma with 71-89% sensitivity and 98-100% specificity.[7] The most important finding from our study was that, the biological behaviour of the tumor is stagnant in progression for which we could make assumption a benignity for its nature. Histopathological examination of the right adrenal tumor specimen after an uncomplicated adrenalectomy confirmed the diagnosis of adrenocortical adenoma.

We have reviewed the treatment of PA elsewhere.[1,5,10] This usually involves either the surgical removal of an adrenocortical tumor or inhibition of renal sodium and potassium exchange by use of spironolactone. Surgery is the treatment of choice once diagnosis of unilateral adrenal tumor has confirmed, though it may not alleviate hypertension in all cases.[1,4] The most common reasons for persistent post-operative hypertension in this case are the number of medication (>2 antihypertensives) and pre-operative longer duration of hypertension (>6 years).[8] Blood pressure becomes normal maximally within 6 months after unilateral adrenalectomy, but some reports indicate that this improvement period can lag up to one year.[5]

Frankly speaking, PA patients display an unfavourable cardiovascular profile, suggesting a role of aldosterone beyond its well-known hypertensive effects1,[8] and surgery offers a therapeutic measure to alleviate aldosterone-associated organ damage beyond its blood pressure reduction. Lin et al. performed a clinical study to investigate LV structure and myocardial fibrosis in 11 patients with PA and their change after adrenalectomy, showing that adrenalectomy reverses LV geometry and alters myocardial texture in PA patients. This advantages can not be shown in spironolactone arm because spironolactone only blocks aldosterone competitively, meanwhile the circulating hormone still in high concentration.[11]

This patients also exhibit a congenital heart disease that mandate its own management. However, atrial septum occlusions before adrenalectomy might delay curative resection, which is problematic because of the time constraints in the management of aldosteronism. This is perhaps the main reason why we decide to performed adrenalectomy in the first priority as the patient is willing to do so and enable for a good candidate for surgery. Right heart

cathetherization will be the next appointment for the patient in the near future.

CONCLUSION

We described a 33 years old female patient who had suffered from intractable hypertension and persistent hypokalemia. Endocrine evaluation suggestive of primary hyperaldosteronisme that later was proved to have an aldosterone-producing adenoma. The standard work-up of patients with primary aldosteronism stressed the role of adrenal CT as the initial investigation of choice and advocate adrenalectomy when the CT reveals unilateral solitary tumor. Diagnosis of this endocrine disorder is essential for the timely initiation of hypertensive therapy and preventing further cardiovascular damage, though a minority of cases, hypertension are not cured by adrenalectomy despite normalization of biochemical tests. Advanced age, duration of hypertension and amount of antihypertensive drugs required to adequately manage the blood pressure may be some factor in this case,[9] however, in general, less medication will be required.

REFERENCES

1. Weiner DI. Endocrine and hypertensive disorders of potassium regulation: Primary aldosteronism. Semin Nephrol. 2013;33:265-76.
2. Conn JW. Primary aldosteronisme: a new clinical syndrome. J Lab Clin Med. 1955;45: 3-17.
3. Mulatero P, Bertello C, Verhovez A, et al. Differential diagnosis of primary aldosteronism subtypes. Curr Hypertens Rep. 2009;11:217-23.
4. Siregar P. Sixteen years experiences in six cases of Conn syndrome in Jakarta. Acta Med Indonesiana 2012; 44(2):150-3.
5. Funder JW, Carey RM, Fardella C, et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2008;93:3266-81.
6. Cely CM, Contreras G. Approach to the patient with hypertension, unexplained hypokalemia, and metabolic alkalosis. Am J Kidney Dis. 2001;37(3):E24-30.
7. Yip L, Tublin ME, Falcone JA, et al. The adrenal mass: correlation of histopathology with imaging. Ann Surg Oncol. 2010;17:846-52.
8. Young Jr. WF. Adrenal causes of hypertension: Pheochromocytoma and primary aldosteronism. Rev Endocr Metab Disord. 2007;8:309-20.
9. Zarnegar R, Young Jr. WF, Lee J, et al. The aldosteronoma resolution score: predicting complete resolution of hypertension after adrenalectomy for aldosteronoma. Ann Surg. 2008;247:511-8.
10. Harris DA, Au-Yong I, Basnyat PA, Sadler GP, Wheeler MH. Review of surgical management of aldosterone secreting tumours of the ad renal cortex. Eur J Surg Oncol. 2003;29:467-74.
11. Lin YH, Lee HH, Liu KL, et al. Reversal of myocardial fibrosis in patients with unilateral hyperladosteronism receiving adrenalectomy. Surgery. 2011;150(30):526-33.