INTRODUCTION

Primary Aldosteronism (PA) is a condition characterized by excessive aldosterone secretion which leads to hypertension and an overall higher risk of mortality from cardiovascular diseases [1]. Conn’s syndrome specifically refers to PA secondary to an adrenal adenoma which is also referred to as Aldosterone-producing adenomas (APA) [2]. The other subtypes of PA include Idiopathic Adrenal Hyperplasia (IAH) which can be unilateral or bilateral, familial hyperaldosteronism (FH) and more rarely ectopic aldosterone secretion from neoplastic disease [3]. The subtypes of PA are an important determining factor for effective management of patients. Unilateral disease is potentially curable with surgery while bilateral disease is treated medically with mineralocorticoid receptor (MR) antagonist. Surgical removal of APA leads to improved cardiovascular outcomes, improvement in hypertension in almost all cases and normalization of potassium level [4]. An important caveat is that the presence of an adrenal adenoma or nodule does not always indicate hypersecretion of aldosterone from the particular growth. Non-functioning adrenal adenomas are a common occurrence especially in older patients [5]. Hypersecretion of aldosterone can be confirmed with a procedure called Adrenal Vein Sampling (AVS). There is known discordance between adrenal imaging with computed tomography (CT) and AVS and the rate is approximately 20-28% [6]. We, therefore, present a case in which such discordance was observed and fortunately the patient was managed appropriately in a tertiary centre with available facilities.

ABSTRACT

Primary aldosteronism (PA) causes a persistently elevated blood pressure (BP) due to excessive release of the hormone aldosterone from the adrenal glands. Classically, it is called Conn’s syndrome and is described as the triad of hypertension and hypokalemia with the presence of unilateral adrenal adenoma. It can be cured with surgical resection of the aldosterone-secreting adenoma leading to resolution of hypertension, hypokalemia and increased cardiovascular risk associated with hyperaldosteronism. We present a case of a man with previous ischemic heart disease (IHD) who presented with resistant hypertension. Investigations for secondary causes of hypertension revealed an elevated aldosterone level and saline suppression test confirmed the diagnosis of PA. Radiological examination revealed a left adrenal adenoma and a normal right adrenal gland. However, adrenal venous sampling showed lateralization of aldosterone secretion towards the right. He subsequently underwent a laparoscopic right adrenalectomy which improved his BP control promptly. This case highlights the importance of recognizing the need to investigate for secondary causes of hypertension. It also underscores the importance of dynamic tests, which may not be easily accessible to most clinicians but should pursue, to allow a definitive diagnosis and effective treatment.

KEYWORDS: primary aldosteronism, hypertension, adrenal adenoma, adrenal vein sampling
CASE PRESENTATION

A 61-year-old man was referred to Emergency Department (ED) with hypertensive urgency. His blood pressure (BP) was 212/112 mmHg on presentation and remained high on consecutive measurements. He denied symptoms of headache, visual disturbance or any neurological deficit. He had been diagnosed with essential hypertension about 5 years prior and his BP had never been optimally controlled. He had stopped taking all his medications which included 2 types of anti-hypertensives in the last 2 years as he had felt well. Other medical problems included a previous history of myocardial infarction requiring angioplasty and stenting 4 years prior, hyperlipidemia and chronic kidney disease (CKD) stage IIIB. There was no previous history of admission to hospital for hypertension related morbidities.

Initial investigations showed serum creatinine of 118µmol/L (NR 62-96) and normal potassium level of 4.5 mmol/L (NR 3.5-5.0). Hemoglobin was 13.8g/dL (NR 12-16) and thyroid function test was normal. There was elevated total cholesterol of 6.8 mmol/L (NR <5.2) and LDL-cholesterol of 5.0mmol/L (NR<2.6). Electrocardiography (ECG) showed normal sinus rhythm with a rate of 80 beats per minute. There were high voltage QRS complexes, ST depression and T-wave inversions in the inferior leads consistent with long standing hypertension and previous history of MI. Echocardiogram showed left ventricular hypertrophy and dilated left ventricle with reduced left ventricular ejection fraction (LVEF) of 46%. He was admitted for a total of 9 days and discharged with a total of 5 anti-hypertensive medications, including Indapamide, Telmisartan, Carvedilol, Felodipine, and Spironolactone.

He was subsequently referred to the Endocrine Unit for further investigations for secondary causes of hypertension. Doppler ultrasound of the kidneys revealed no evidence of suprarenal mass or renal artery stenosis and both kidneys were of normal size. 24-hour urinary cortisol level was normal at 719.6nmol/day (NR: 53.2 – 876.3) as well as 24-hour urinary catecholamine levels. Urinary epinephrine was 1.8 µg/day (NR: 0.5 – 20), urinary norepinephrine of 36.7µg/day (NR: 15 – 80) and urinary dopamine level was 143 µg/day (NR: 64 – 400). His anti-hypertensive medications were ceased and replaced by high doses of prazosin and felodipine. Subsequent investigations demonstrated an elevated serum aldosterone of 924 pmol/L (NR: 111 – 860) with suppressed plasma renin activity of 0.4ng/ml/hr (NR: 1.5 – 5.7) with an aldosterone to renin ratio of 2060 (NR <750). A Saline Suppression Test (SST) was performed with the administration of one litre of intravenous saline over 4 hours. The results were as follows: pre-saline aldosterone level of 995 pmol/L (NR: 111 – 860); post-saline aldosterone of 511 pmol/L (NR < 140). A non-contrasted computed tomography (CT) of the adrenal glands revealed a left adrenal adenoma measuring 1.4cm x 1.5cm with a Hounsfield Unit (HU) of 12 and absolute washout of 60% (Figure 1). The right adrenal
gland was slightly bulky, but normal in appearance with no focal lesion within. Surgical resection of the adrenal adenoma as a potential treatment option was discussed and patient was keen to proceed.

Adrenal venous sampling (AVS) was later performed by an interventional radiologist with cosyntropin stimulation [7]. The procedure involved cannulation of the inferior vena cava (IVC) initially and then sequentially both right and left adrenal veins. Measurement of both cortisol and aldosterone level are performed with each cannulation. The ratio between cortisol levels between each adrenal vein (left and right) and IVC confirms the accuracy of cannulation into the adrenal veins. This is called Cannulation Index (CI) and a CI of 2-3 is adequate. The ratio of aldosterone and cortisol levels (AC ratio) between the two adrenal veins gives the lateralisation index (LI) which proves which adrenal gland is hypersecreting aldosterone. A ratio of 3-5 is considered adequate to prove lateralisation [7].

The results of the AVS showed a CI of 15 for the right side and 23 for the left indicating adequate cannulation. There is a LI ratio of 8.6 towards the right adrenal gland which is significant at 8:1 (Table 1). The patient subsequently underwent a repeat AVS to ascertain the findings, which produced similar results.

<table>
<thead>
<tr>
<th>Vein</th>
<th>Aldosterone (A), pmol/L</th>
<th>Cortisol (C), nmol/L</th>
<th>A/C ratio</th>
<th>LI ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Adrenal Vein</td>
<td>90,265</td>
<td>8684</td>
<td>10.4</td>
<td>8.6</td>
</tr>
<tr>
<td>Left Adrenal Vein</td>
<td>15,848</td>
<td>13,699</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Inferior Vena Cava</td>
<td>1,674</td>
<td>591</td>
<td>2.8</td>
<td></td>
</tr>
</tbody>
</table>

He underwent a successful laparoscopic right adrenalectomy one month subsequent to the AVS results and recovered well. Gross examination of the excised adrenal gland (measuring 45x22x10 mm) revealed a single, well defined yellowish nodule (10x7x5 mm) located on one side of the gland. Microscopically, this nodule was encased in a thin, delicate capsule; it contained cells with round nucleus surrounded by foamy cytoplasm mixed with lesser number of cells with eosinophilic cytoplasm. Mitosis and atypia were absent. The rest of the gland showed normal histology. The overall histological features are in keeping with an adrenal cortical adenoma (Figure 2).

Subsequent clinic visits post-surgery revealed stable BP control. He is currently well, requiring only low doses of 2 anti-hypertensive agents which are carvedilol and felodipine.

Figure 2 (a) Gross examination of the adrenal gland revealed a well-defined nodule on one side of the gland (black arrow), the rest of the adrenal cortex was normal, with no evidence of hyperplasia (red arrow). (b) Photomicrograph showed a well circumscribed nodule (arrow) surrounded by a thin rim of fibrous tissue (Haematoxylin and Eosin (H&E), magnification 40X); (c) the cells within the nodules are composed polygonal cells with round nucleus and foamy cytoplasm (H&E, magnification 400X); (d) the rest of the adrenal gland show normal morphology (H&E, magnification 40X).
DISCUSSION

This case firstly highlights the importance of identifying the rarer condition of hyperaldosteronism in a seemingly common disease of hypertension. There should be a high degree of suspicion for secondary causes of hypertension in patients with resistant blood pressure controls. Clinicians should be vigilant of patients requiring 3 or more anti-hypertensive medications as this indicates resistant hypertension. A previous diagnosis of essential hypertension should not deter clinicians from conducting further investigations to rule out both structural or hormonal abnormalities. However, it is imperative to rule out pseudoresistance factors such as white coat hypertension, non-compliance to medications and inaccurate blood pressure measurement [8].

Resistant hypertension has a myriad of causative factors. Structural abnormalities such as renal artery stenosis (RAS) and coarctation of the aorta may be present and easily diagnosed with imaging techniques such as doppler ultrasonography and computed tomographic angiography (CTA) respectively [9]. Only 10% of RAS cases are derived from fibromuscular dysplasia which classically affects females less than 50 years of age [10]. RAS occurs most commonly in the elderly populations especially smokers and those with pre-existing atherosclerotic disease. This is especially relevant as it fits the demographics of this case and therefore has been adequately assessed.

Hormonal abnormalities resulting in resistant hypertension can be due to PA, phaeochromocytoma, or Cushing’s syndrome. All of the three aforementioned conditions are associated with hypersecretion from an adrenal adenoma and is particularly relevant in this case. An adrenal adenoma can be present and be a non-functioning nodule and this is termed adrenal incidentiloma. It is a common occurrence in the older age group of >40 years of age and is usually identified during imaging that is performed for indications not related to investigation of resistant hypertension. Biochemical investigations to screen for hormonal excess causing resistant hypertension are crucial to determining the diagnosis and excluding adrenal incidentilomas.

Phaeochromocytoma is a rare disease with a prevalence of <1% of the hypertensive population. Its clinical manifestation include episodic symptoms of headache, palpitations and sweating with concomitant resistant hypertension [11]. A highly sensitive test for screening is 24-hour urinary metanephrines or plasma free metanephrines [12]. As for Cushing’s syndrome, screening involves either a 24-hour urinary free cortisol, late-night salivary cortisol or 1-mg overnight dexamethasone suppression test [13]. Hypercortisolism from Cushing’s syndrome results in specific clinical features such as central obesity, moon face, easy skin bruising, purple striae and proximal muscle weakness. Hypertension is a major component of Cushing’s syndrome and it is due to water retention and volume expansion related to excess cortisol [14].

PA is the commonest hormonal abnormality resulting in resistant hypertension. The estimated prevalence of PA in hypertensive population is between 5% to 13% [15]. According to the 2016 Endocrine Society Clinical Guideline for the diagnosis of PA, all patients with hypertension requiring 3 or more anti-hypertensive medications should be screened for PA [15]. Other indications include hypertension accompanied by sleep apnea, presence of family history of premature IHD or stroke (<40years) and with known first-degree relative with PA [15]. The same clinical guideline also clearly outlines the necessary processes for diagnosis and management of PA.

Initial screening test is done with serum aldosterone paired with direct renin level. In order to achieve a useful result, several anti-hypertensive medications need to be discontinued. These medications can cause false positive or false negative results. The medications are ACE-Inhibitors, Angiotensin-Receptor Antagonist, Beta-blockers, Mineralocorticoid Receptor Blockers and Diuretics [15]. A positive screening test would be an elevated aldosterone level and low renin, with an aldosterone to renin ratio of >750. Confirmatory tests are mandatory after a positive screening test. A commonly used test is the saline suppression test which would show failure of aldosterone suppression with salt loading. This establishes the diagnosis of PA.
The decision to screen for PA can be influenced by other supporting factors such as age and presence of hypokalemia. International guidelines have outlined the need for screening for secondary causes of hypertension among younger patients below the age of 40. This case not only affirms that statement but also emphasizes that decisions to screen patients should be based on individual needs and not restrict to only those below 40 years of age. Also, the presence of hypokalemia is a strong predictor for PA but it is only present in severe disease. Despite previous understandings of hyperaldosteronism, more recent data have indicated that hypokalemia only occurs in 9 to 37% of patients with confirmed PA [15]. Thus, the majority of patients with PA may have normal potassium levels as demonstrated in this case. The normal potassium level may have delayed the detectability of the underlying condition. However, this should no longer be an exclusion to proceed with further investigations for PA. Early detection and treatment of PA is pivotal in cardiovascular risk reductions such as stroke and IHD [16].

After establishing the diagnosis of PA, the next step is to determine the disease subtype. This is crucial as the different subtypes of PA have distinct treatment options. The process of subtyping is by imaging with CT scan to assess for the presence of adrenal adenoma. The presence of adrenal adenoma; either unilateral or bilateral as well as the patient’s preference for surgical intervention determines subsequent management options. If surgical intervention is not desired in unilateral disease or there are bilateral adenomas, medical treatment with MR antagonist is commenced. In unilateral adrenal adenoma with surgery as a treatment option, lateralization is done with AVS [15]. AVS is used to localize and lateralize aldosterone hypersecretion. It is a highly specific procedure and requires high technical expertise albeit with varying success rates, thus rendering it not widely available [17]. Once lateralization is confirmed and consistent with the presence of an adenoma, surgery can proceed and patient can potentially be cured.

The most significant impact of this report is the benefit and necessity of AVS towards achieving the best treatment option for this patient. AVS is recommended for lateralization as the accuracy of imaging is only about 50% [18]. This is partly attributed to the rise in adrenal incidentilomas especially in older populations. This discordance between imaging with CT and AVS in lateralization of PA is well documented. A recent study showed the discordance rate was 20-28% and related to both imaging and AVS factors [6]. The discordance can be attributed to operator-dependant expertise in AVS techniques and also variable interpretation criteria. The adequacy of AVS is important to address as it is a factor in the discordance between imaging and AVS [6]. The accuracy of AVS can be improved by a repeat procedure, ensuring adequate cannulation of the adrenal veins and also using a less stringent LI ratio during interpretation [6]. Thus, this case emphasizes a pertinent issue of providing the most effective management. The patient could have had an inappropriate removal of the left adrenal incidentaloma, had the AVS not been or inadequately performed. That would have resulted in a futile surgery and he would have consequently required a second adrenalectomy on the contralateral side, leaving him with absolute hypocortisolism and requiring life-long hydrocortisone replacement.

CONCLUSION

In conclusion, identification of resistant hypertension is essential in order to identify secondary causes of hypertension. Hormonal causes to be considered are PA, phaeochromocytoma and Cushing’s syndrome especially in the presence of an adrenal adenoma. The diagnosis of PA requires a high degree of clinical suspicion and should be prioritized to individual patients. Early detection and treatment may confer significant benefits. Age below 40 and presence of hypokalemia are no longer absolute requirements for screening for PA. Screening for PA should be done in patients who have resistant hypertension requiring more than three anti-hypertensive medications. Upon confirmation of hyperaldosteronism, radiological imaging is indicated but not limited. Adrenal venous sampling, if indicated, must be pursued to ensure accurate lateralization and subsequent effective surgical treatment.

Conflict of Interest

Authors declare none
Acknowledgement

We would like to thank all clinicians involved in the care of this patient as well as the patient for his cooperation in providing clinical information.

REFERENCES