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Case Report

Adrenal gland-sparing transcatheter embolisation of an aldosteronoma for the treatment of refractory hypertension ☆

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ABSTRACT

In patients with hypertension secondary to aldosterone secreting adrenal adenomas, medical and surgical treatments are both well described, with trans-catheter arterial embolization an uncommon form of therapy, currently. In patients where medical therapy has not provided sufficient response, and where surgical therapy is not deemed appropriate, trans-catheter arterial embolization of aldosteronomas has shown promise in a number of case series. We present the case of a 69-year-old man with hypertension refractory to medical therapy, and deemed not to be a surgical candidate for laparoscopic adrenalectomy. The patient underwent successful selective embolization of a functional adrenal adenoma, with sustained improvement in his prior hypertension, and without major complication. We conclude that trans-catheter embolization, when performed in the carefully selected suitable candidate, is a promising therapeutic option, and warrants a cohort study to assess long term outcomes.

Introduction

Non–suppressible primary hypersecretion of aldosterone, or primary aldosteronism (PA) is an increasingly recognized cause of hypertension, and in approximately 30% of cases, is due to unilateral aldosterone producing adenomas (APA) [1] or else by bilateral adrenal hyperplasia, sometimes with nodular hyperplasia. PA is a common form of secondary hypertension, with suggestions it accounts for as much as 4% of hypertensive patients in primary care, and up to 10% of specialist referred patients [2].

When caused by unilateral APA, it may be treated medically, typically by mineralocorticoid receptor antagonists (MRA), or surgically by laparoscopic adrenalectomy. More recently treatment by super selective adrenal arterial emboliza-

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tion (SAAE), has been described, and a case series of 33 published by Hokotate et al in 2003 [3] is the largest published cohort to our knowledge.

The typical indications for adrenal artery embolization are oncological debulking or devascularization, control of retroperitoneal hemorrhage, and suppression of adrenal hormone production [4].

Treatment of refractory hypertension secondary to APAs with SAAE is typically a low risk, low morbidity procedure in the correctly selected patient, with the appropriate workup. The patient workup typically involves assessing the functionality of an adrenal gland nodule which is discovered by computed tomography (CT) of the abdomen, followed by bilateral adrenal vein sampling (AVS). AVS is required to lateralize the adenoma as the functional cause of PA, which is done by calculating the lateralization index (LI), using bilateral adrenal vein sample concentrations of plasma aldosterone and cortisol levels [5]. Once autonomous adrenal gland function has been proven (usually by failure to suppress plasma aldosterone with intravenous saline), and lateralization confirmed by AVS then embolization can be considered.

The specific adrenal arterial branches which supply the functional adenoma are localized by catheter angiography, if not previously seen on CT angiography. Various embolic agents, including coils, alcohol particles, high concentration ethanol, glue, and patent microspheres have been used in adrenal gland embolization procedures.

The rich collateral arterial blood supply of the gland, which typically involves 3 main adrenal arteries, which branch into between ten and twenty smaller glandular branches, means that super selective embolization of an adenoma is unlikely to result in adrenal gland infarction and necrosis, and the release of significant catecholamines or adrenal insufficiency. Previously described complications include mild or moderate flank and back pain, persistent hiccups, transient hypertension or lability of blood pressure, transient pleural effusion, and transient low-grade fever [3,4,6].

No large-scale studies comparing SAAE with current medical and surgical therapies exist, and no controlled trials have been conducted. The results from previous case-series are promising, with the 2003 Hokotate et al series of 33 patients showing biochemical success in 82% of patients. Clinical success in terms of hypertension was age dependent, with 100% of patients aged under forty-five years having persistent reduction, and 50% of patients aged over forty-five.

Smaller other case series have been performed, and a small number of recent case reports have been published.

Case report

A 69-year-old man was seen in a renal and hypertension clinic due to longstanding hypertension in the context of a recently diagnosed left adrenal adenoma. An adrenal nodule had been identified incidentally 6 years prior on a CT of the abdomen for abdominal pain, demonstrating a perinephric hematoma. The 1.7 cm left adrenal gland nodule (see Fig. 1) subsequently underwent further investigation with 3 further CT scans, over the course of 3 years, which demonstrated size stability over time,

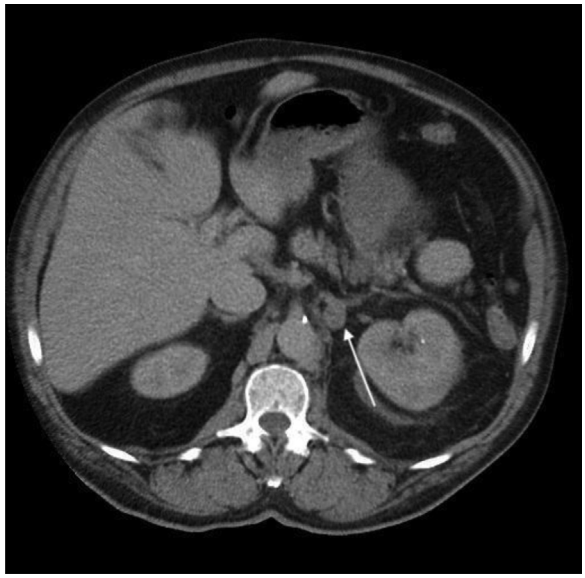

Fig. 1 – Axial CT image demonstrating an incidental left adrenal gland nodule (white arrow).

and an absolute percentage washout (APW) of 69%, which is typical of adrenal gland adenomas [7].

The patient was managed for PA medically, and had been previously considered for laparoscopic adrenalectomy, though this was not carried out, given his co-morbid medical history which included type 2 diabetes mellitus, severe sleep apnea, atrial fibrillation, diastolic heart failure, and mitral regurgitation.

Whilst there was some early success in BP control, this did not last and at the time of the referral for embolization, his blood pressure remained elevated at 165/98 mm Hg despite treatment with eplerenone 200 mg in the morning and 100 mg at night, furosemide 40 mg in the morning, and 20 mg at midday, ramipril 10 mg in the morning, irbesartan 300 mg at night, amiloride 5 mg twice daily and he was hypokalemic to 3.1 mmol/L, despite 6 tablets daily of chlorvescent. Following hospitalization due to a symptomatic episode of diastolic heart failure, further consideration was given to laparoscopic adrenalectomy- though was not carried out given medical co-morbidities, and further investigations at this time revealing left ventricular hypertrophy, moderate mitral regurgitation, and elevated pulmonary pressures. He was subsequently referred for consideration of SAAE.

CT angiography demonstrated conventional adrenal arterial anatomy, with 3 arteries, arising from the inferior phrenic, the aorta, and left renal artery. The aortic branch appeared to be at least partially stenosed

Adrenal vein sampling

The right adrenal vein was sampled with a 7-french Mach 1 catheter (Boston Scientific, Marlborough, MA), and the left adreno-phrenic venous trunk via a Sim-2 Glidecath (Terumo, Shibuya-ku, Tokyo), via a 7-french sheath (Cook Medical, Bloomington, IN) in the right common femoral vein (CFV). Three samples were obtained from each adrenal vein, and a

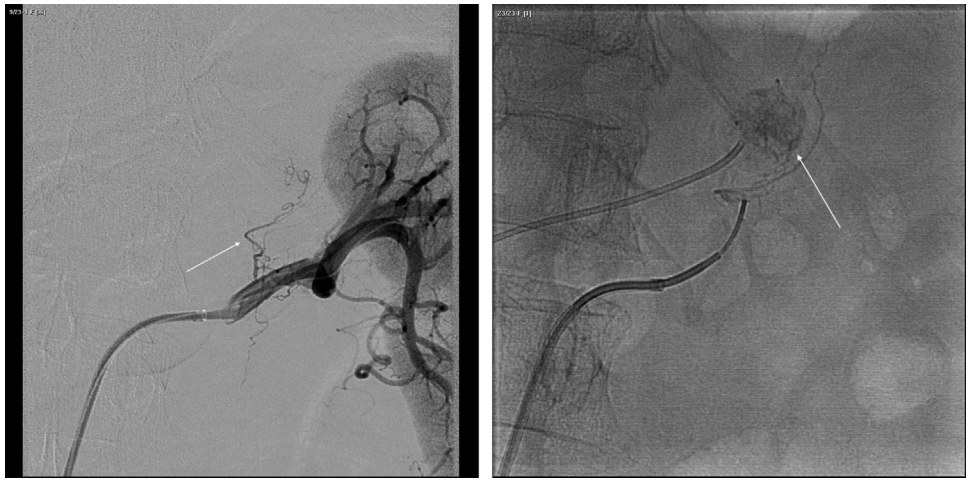

Fig. 2 – A (left) and B (right) Catheter angiography showing the left inferior adrenal artery (white arrow) arising from the mid-left renal artery, and contrast staining of the adenoma(white arrow) following super-selective micro-catheterization of the branches of the inferior adrenal artery.

sample from each of the supra-renal SVC, infra-renal SVC, and peripheral venous sample from the right median cubital vein.

The left adrenal gland nodule was confirmed as a functional aldosteronoma, with left adrenal vein samples showing aldosterone levels >99999 pmol/L, and the right adrenal vein samples all below 5000 pmol/L. The 2 IVC, and peripheral venous samples all showed aldosterone levels between 2000 and 2300 pmol/L, and all of the acquired samples showed renin levels <1 mU/L. The LI was calculated using the method detailed by Rossi et al in 2014. Current literature suggests an LI of >2 as positive for lateralization where cosyntrophin stimulation is not used, and LI>4 where it is used. There is no compelling evidence that use of stimulation improved lateralization outcomes [5]. The LI calculated in the current case was 134. The patient underwent the AVS procedure as a day-only patient, without sedation and was discharged on the same day without complication.

Adrenal embolization

The patient subsequently underwent left aldosteronoma embolization under general anesthesia, with anesthetic support given the risk of blood pressure lability or hypertensive crisis. Super-selective catheterization of the left adrenal arteries was performed with 7-French Mach-1 Guide catheter (Boston Scientific, Marlborough, MA), 5-french Ka catheter (Merit Medical, South Jordan, Utah), and 2.4fr Progreat microcatheter (Terumo, Shibuya-Ku, Tokyo), via a 7-french sheath (Cook Medical, Bloomington, IN) in the right common femoral artery (CFA). The arterial supply to the APA was defined from the inferior adrenal artery arising from the mid left renal artery, confirmed by angiography and cone-beam CT (Fig. 2). The superior adrenal gland artery supplied the majority of the remainder of the gland (Fig. 3), and the middle supplied modest contribution, with significant stenosis at the origin (Fig. 4)

The adenoma was embolized using 1.5 mLs of 3:1 ethanol and lipiodol, and post-embolization lipiodol staining of the adenoma was confirmed by cone-beam CT (Fig. 5). The rate of injection was approximately 0.25 mLs/min. During the embolization, the adrenal vein was aspirated using a Sim-2 Glidecath (Terumo, Shibuya-Ku, Tokyo) in the left adrenal vein, introduced via a 5-french introducer sheath (Cook Medical, Bloomington, IN) in the left CFV (see Fig. 2) . We performed this novel technique to minimize the probability of a hypertensive crisis secondary to aldosterone, cortisol, and possible catecholamine release during embolization.

The patient did not experience any hypertensive crisis during the procedure, though was hypertensive to 190/100 mm Hg

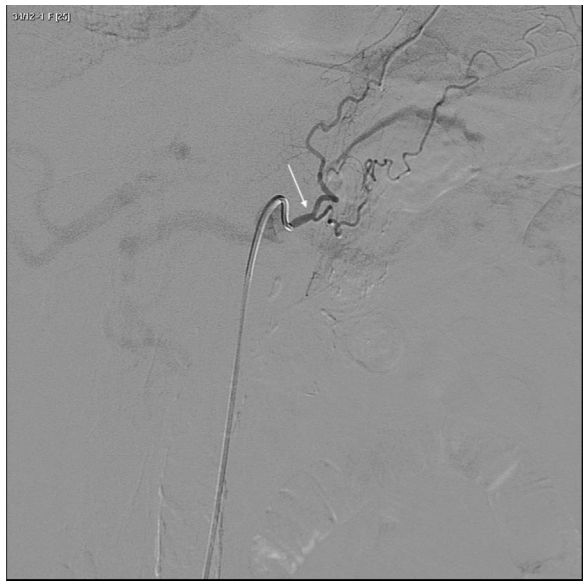

Fig. 3 – Catheter angiography of the left inferior phrenic artery (white arrow), supplying the main parenchyma of the left adrenal gland.

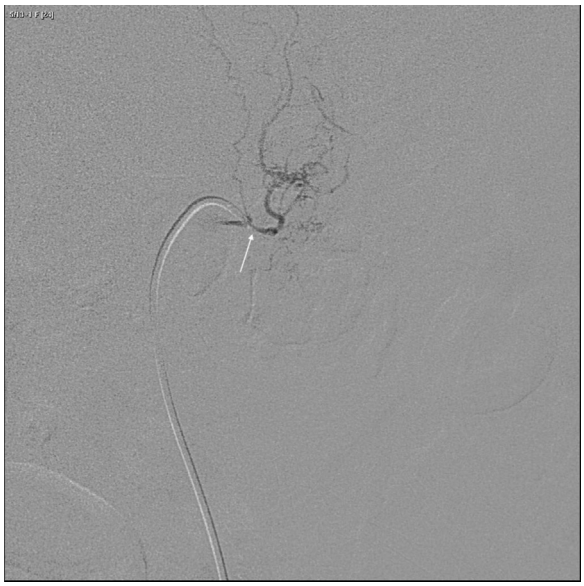

Fig. 4 – Catheter angiography of the middle left adrenal artery, showing stenosis (white arrow) at the origin, and no appreciable staining of the adenoma.

approximately 6 hours later in recovery, and was treated with a single dose of 10 mg of IV phentolamine, after which this improved to his baseline of 160/90 mm Hg. He was admitted to the intensive care unit (ICU), for invasive blood pressure monitoring during the post-procedural period. All usual antihypertensives were given in ICU, though the patient's furosemide and amiloride were not given. The highest blood pressure recorded was 173/98 mm Hg, prior to the patient's morning antihypertensive doses, on the day following the procedure. No additional hypertensive treatments were administered during the remainder of the ICU admission. The patient was hypokalemic to 2.6 mmol/L, and was supplemented with intravenous potassium, after which this improved to 3.5 mmol/L. He was discharged from ICU and hospital after 48 hours.

At the initial 10 day follow up, the patient's blood pressure had improved to 122/86 mm Hg, and the serum potassium to 4.1 mmol/L. The eplerenone dose was lowered to 100 mg twice daily, and the oral potassium supplementation was ceased. Following an episode of symptomatic hypotension of 81/59 mm Hg, within 1 month, all further antihypertensives were ceased, apart from 10 mg of daily ramipril, and 12.5 mg of daily chlorthalidone, which was newly prescribed for peripheral oedema . 24-hour ambulatory blood pressure monitoring at 6 months was 117/82 mm Hg, and at 10 month follow up the blood pressure remained 134/84 mm Hg, and serum potassium remained normal at 4.1 mmol/L.

Abdominal CT imaging follow up at 1 month post procedure, demonstrated fossilization of the aldosteronoma, with sparing of the remainder of the left adrenal gland parenchyma (Fig. 6). It measured 15 mm at that stage. A CT of the abdomen at 11 months post procedure, demonstrated involution of the fossilized aldosteronoma, measuring 10 mm at that stage (Fig. 7).

Discussion

PA is an increasingly recognized and investigated cause of hypertension accounting for a large proportion of cases of secondary hypertension. The significantly increased cardiac and renal related morbidity and mortality of the disease, even where hypertension is well controlled medically, has been the subject of recent investigation, and is summarized well in the review by Vaidya et al in 2018 [5].

Aldosterone is known to modulate other cardiac risks apart from high blood pressure. Notably the incidence of cardiac events, incident mortality, diabetes, and atrial fibrillation have been found to be higher in patients with PA on MRAs where renin remained suppressed, compared with patients with essential hypertension, where blood pressure and other cardiovascular risks were the same in both groups [9]. There is a growing body of evidence suggesting that removal of the source of autonomous aldosterone production leads to improved long term cardiac outcomes [10,11].

In the present case, we performed, to our knowledge, the first published case of SAAE in Australia. We employed selective embolization of the aldosteronoma, sparing the remainder of the adrenal gland. We employed a novel technique of adrenal vein aspiration whilst the embolization was performed, to decrease the risk of hypertensive crisis. There were no episodes of severe hypertension during the procedure, and apart from a single short-lived episode of hypertension 6 hours after the procedure, there were no other episodes post procedurally. There were no complications apart from mild transient flank pain, and the patient was discharged from hospital within 48 hours. In further investigation of SAAE, we are interested to examine whether this technique, the adrenal vein sump, has a lesser incidence of hypertensive crises than cases in which it is not employed.

Current reviews and clinical guidelines on the topic of PA generally recommend laparoscopic adrenalectomy where it is secondary to an adenoma or unilateral hyperplasia, or medical management where this is not possible [1,2,8,12]. SAAE is not recommended or mentioned in these reviews and guidelines. The only interventional radiology technique mentioned is percutaneous CT guided ablation, which is recommended against [1], and the use of adrenal vein sampling to localize either a functional adenoma, or unilateral adrenal hyperplasia as a cause of PA [12].

An international consensus on outcomes after adrenalectomy for unilateral PA found complete clinical success in 37% and partial clinical success in 47% of the included 705 patients. Adrenalectomy is currently considered the gold standard, with an existing body of evidence [13]. Evidence for the efficacy of SAAE is lacking, with no large-scale trials or cohort studies, and no comparative analysis available to our knowledge. The case series of 33 by Hokotatae et al (2), did show promising results however. Careful patient selection and detailed work up of possible candidates is proving to be important at these early stages. The age-dependence of clinical response to the procedure in previous cases, is worth consideration. The angio-anatomy is also unlikely to be suitable in some patients, and workup with dedicated CT angiogram, and possibly catheter angiogram, is warranted to assess suitabil-

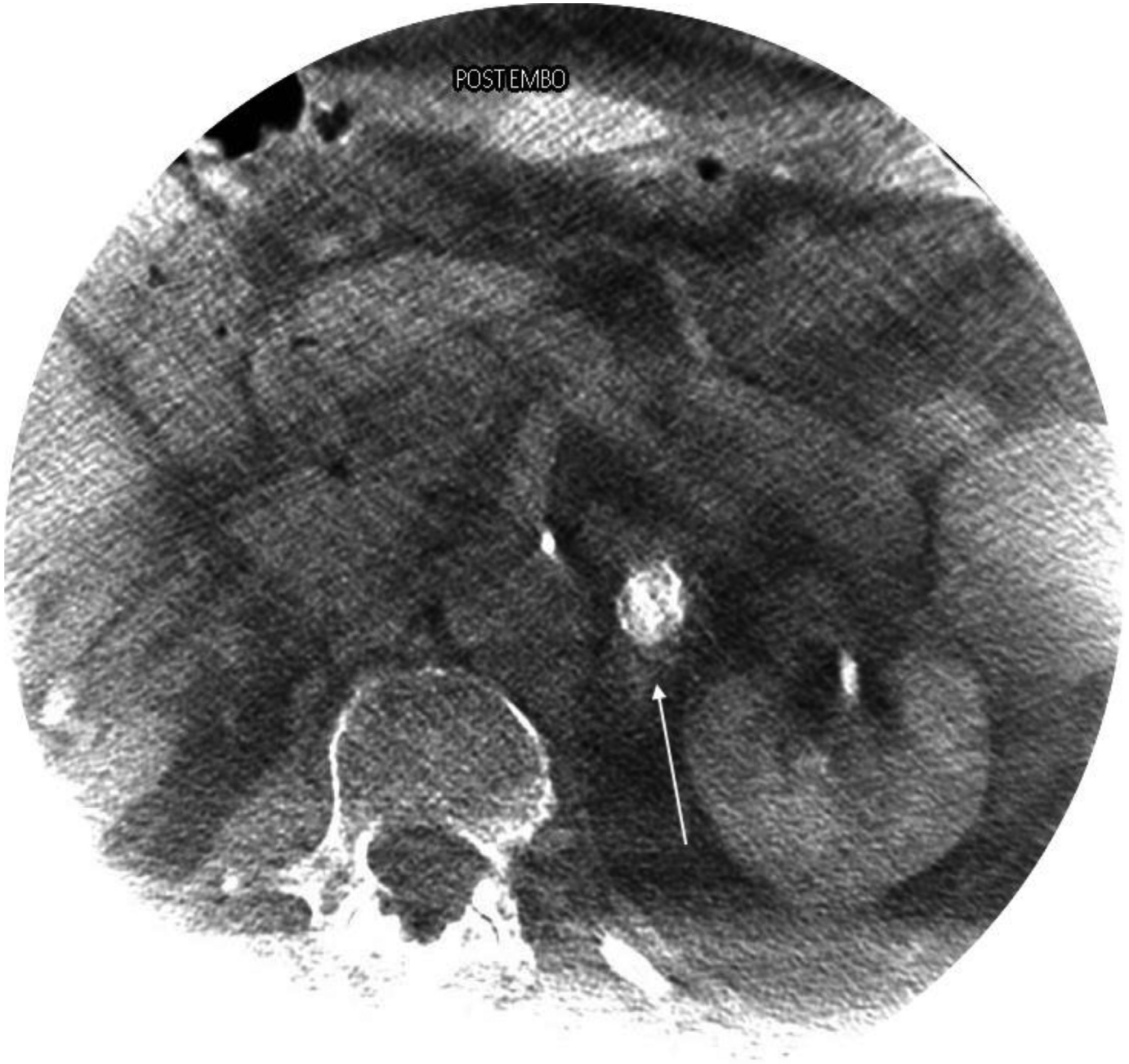

Fig. 5 – On table cone-beam CT demonstrating lipiodol staining (white arrow) of the left adrenal gland aldosteronoma following embolization with ethanol and lipiodol.

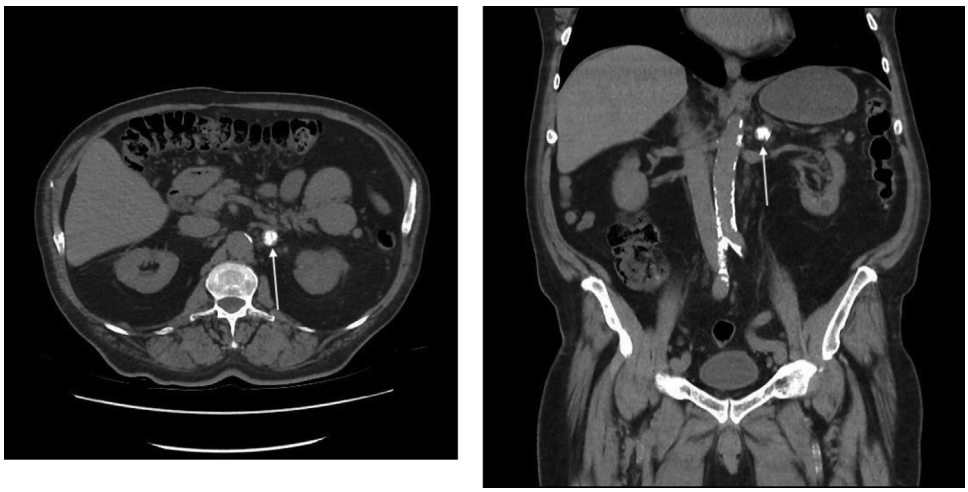

Fig. 6 – A (left) and B (right) Axial and coronal projection CT images demonstrating the fossilized left adrenal aldosteronoma (white arrows) at 1 month after the embolization procedure.

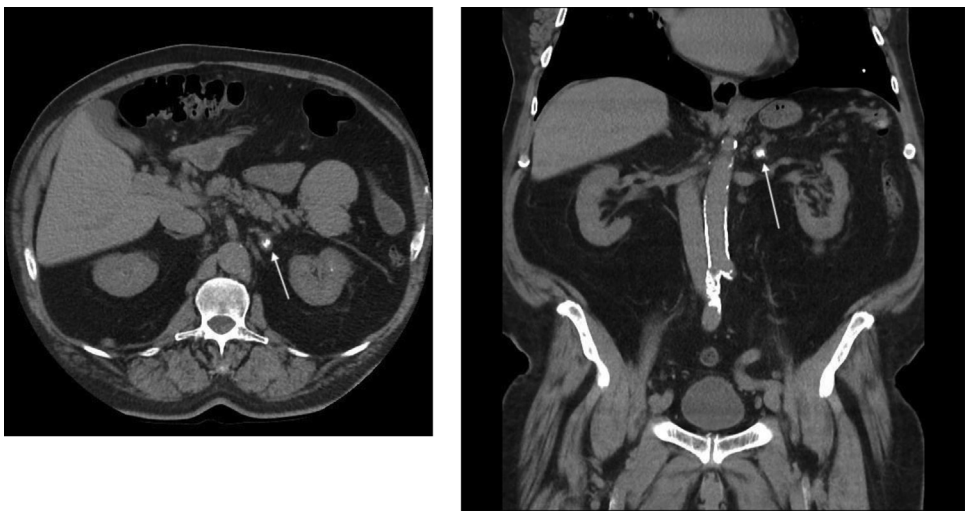

Fig. 7 – A (left) and B (right), Axial and coronal projection CT images demonstrating the fossilized left adrenal adenoma 11 months following the embolization procedure, which had undergone reduction in size from 15 mm to 10 mm over this period.

ity. In the current case, the anatomy was such that the aldosteronoma had well delineated arterial supply which allowed super selective embolization, whilst sparing the remainder of the adrenal gland. This likely contributed to the success of the case, and further supports the notion that patient selection will need to be based on relatively extensive pre-procedural investigation, which may need to include catheter angiography if CT angiography is inconclusive.

There are some potential advantages of SAAE over laparoscopic adrenalectomy in selected patients. The relatively rare adrenalectomy complications detailed by Raffaelli et al [14] are: bowel and vascular injuries, operative difficulties related to adhesions and obesity, liver injury, duodenal injury, division of a renal polar artery, rupture of the adrenal capsule, and injury to the diaphragm, and injury to the spleen and pancreatic tail. These have not been reported in SAAE. The rate of adrenalectomy complications is estimated to be low, at less than 9%, and the typical hospital stay also low, at 3.9 days [14]. Air embolism and non–target embolization would be considered relatively unique to SAAE, though no serious cases of the same have been reported to date. The current case underwent a general anesthetic, and was monitored in ICU post-procedurally. With increased local experience, these may be considered less necessary, as has been the experience of others [4].

This current case demonstrated clinical and biochemical success with follow up at 10 months, in a patient who was a high-risk surgical candidate, with no significant procedure related morbidity. Given the growing body of evidence suggesting that patients with PA have poor cardiovascular outcomes despite adequate control of hypertension, we suggest that patients with functional aldosteronomas, who are not

suitable for adrenalectomy, should be considered for SAAE, and a cohort study of these patients' long-term outcomes is warranted.

Patient consent

Written consent was obtained from the patient who is the subject of this case report. No identifiable information about the patient has been included in the case report. A written and signed copy of the patient consent has been retained by the authors of this publication for record keeping.

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