Pathways and dead ends in the diagnostics of primary aldosteronism

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Abstract

We present a patient with a tumour of the left adrenal gland who has been treated for resistant hypertension and hypokalaemia for years. Primary aldosteronism was confirmed, but despite multiple attempts at adrenal vein sampling we were unable to prove unilateral disease. Treatment with mineralocorticoid receptor antagonists was not successful, however no clear indication for surgical treatment was present. Patient's clinical and laboratory characteristics pointed to unilateral disease, so he was referred for PET CT with 11-C-metomidate in the United Kingdom. Unilateral disease was confirmed, and the patient was cured by left-sided laparoscopic adrenalectomy.

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1 Introduction

Arterial hypertension (HTN) is a condition where systemic arterial pressure is permanently elevated to 140/90 mmHg or more. The incidence of HTN increases with age. In Slovenia, it is found in about 60 % of the adult population (1). In about 90 % of cases, we are referring to primary (essential) HTN, which is due to the complex interactions of genetic and environmental factors (2). Appropriate measures help us achieve blood pressure (BP) targets below 140/90 mm Hg, thereby reducing the incidence of serious cardiovascular events (1). Secondary HTN has a known cause for high BP. Although the proportion of these patients is only about 10 %, it is important to recognize them, since they suffer from a reversible condition that can be cured permanently by eliminating the cause (3). The most common cause of secondary hypertension is usually primary aldosteronism (PA) (4).

PA can be described as an autonomic and excessive secretion of aldosterone from the adrenal cortex (5). There are two main forms of illness, namely, the bilateral idiopathic hyperaldosteronism (IHA) and the unilateral aldosterone-producing adenoma, APA, or Conn's syndrome. The unilateral form of the illness may rarely be also caused by adrenocortical carcinoma that secretes mineralocorticoids, and more often by

the primary unilateral adrenal hyperplasia, where the clinical treatment is the same as in APA (6). A disrupted negative feedback loop in PA results in water and sodium retention, as well as the increase in BP, and, in severe cases, the occurrence of hypokalaemia and metabolic alkalosis (5,7).

PA is found in about 6 % of hypertensive patients who are treated at the primary level of healthcare. The incidence of the disease increases with the severity of hypertension, in a recent study, for example, from 3.9 % in stage 1 hypertension to 11.8 % in stage 3 hypertension (8). Elevated BP is usually the only PA presentation, so the disease is often overlooked (9).

This is important because unrecognized PA causes higher morbidity and mortality than the equally severe essential hypertension. Long-term exposure to high levels of aldosterone is harmful to the cardiovascular system and kidneys. Patients with PA compared with patients with essential hypertension are more likely to suffer from arrhythmias, coronary artery disease, heart failure, myocardial infarction, proteinuria, and renal failure (5). There is also a greater prevalence of metabolic syndrome (6).

The Endocrine Society therefore recommends screening high-risk population for PA, which includes patients with hypertension and spontaneous or diuretic induced hypokalaemia, resistant hypertension, hypertension with an adrenal incidentaloma, with a sustained blood pressure above 150/100 mmHg, hypertension and obstructive sleep apnea, hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (< 40 years) and all hypertensive patients that have first-degree relatives with PA (5).

Aldosterone/renin ratio (ARR) (plasma aldosterone concentration (PAC) divided by plasma renin activity (PRA)) is used for screening. ARR values above 1 nmol/L per μg/L/h are suspicious for autonomic secretion of aldosterone if PAC is relatively high, e.g. greater than 0.3 nmol/L. A possible hypokalaemia should be corrected before determining ARR, and, mineralocorticoid receptor antagonists (MRA) should be stopped for at least the last four weeks. If possible we also withdraw other diuretics two weeks prior to testing, whereas all other antihypertensives with the exception of non-dihydropyridine calcium antagonists, alpha blockers and moxonidine, should only be stopped in the case of a high clinical suspicion of PA and negative hormonal findings. PA is finally confirmed by one of the confirmatory tests. In our patients, two litres of saline solution is administered intravenously within four hours. PA is confirmed if PAC does not decrease below 0.14 nmol/L after the test (5).

Unilateral PA treatment is primarily surgical with a laparoscopic adrenalectomy, and bilateral PA with spironolactone or other MRAs. In the event that the patient disagrees with the surgery or is not a suitable candidate, unilateral PA is also treated with MRA (4). Genetic testing for familial hyperaldosteronism, which is also treated medically, is performed in patients with PA younger than 20 years or with a family history of PA or stroke before the age of 40 years (6).

If a patient with a confirmed PA wants surgery, it is then crucial to differentiate between unilateral and bilateral forms of the disease. First, we perform an adrenal CT scan to exclude a larger tumor that could present an adrenocortical carcinoma, followed by adrenal vein sampling (AVS) (5). This is a diagnostic procedure where an interventional radiologist takes a blood sample via a femoral vein to determine the concentration of aldos-

terone and cortisol first from the right and then the left adrenal vein, and last, from vena cava inferior (VCI). Technical successfulness of AVS is checked by calculating the selectivity index (SI), i.e. the ratio of cortisol concentrations in the adrenal vein and in the VCI, which must be above 5 if the test is performed under ACTH stimulation, as in our institution. The decision on the type of treatment is then influenced by the calculation of the gradient of the aldosterone/cortisol ratio between ipsilateral and contralateral adrenal vein, i.e. the lateralization index (LI). Values over 4 speak for a unilateral PA form (10). AVS is an invasive, technically complex, and expensive diagnostic test, but due to its high sensitivity and specificity, it is a gold standard for differentiating between the two main forms of PA (4,5). If AVS reliably confirms a unilateral disease, we are able to normalize patients' BP with laparoscopic adrenalectomy in approximately 40 % of patients, and significantly facilitate HTN management in the vast majority of others. The surgery is more successful in younger patients and in women, whereas the results are poorer in patients with long-standing HTN (> 10 years), familial HTN, higher body mass index, poor renal function, and a greater number of antihypertensive drugs used before the adrenalectomy (11,12).

Because PA is common, the path to surgery relatively complex, and its success dependent on many factors, we always adjust the extent of diagnostics individually. In the elderly with suspected PA and many comorbidities, after determining the ARR, or even without testing, we may introduce a MRA at a low dose if the renal function permits. Imaging diagnostics is only necessary in such patients if they have a markedly high blood pressure and/or severe hypokalaemia in order not to overlook an adrenocortical carcinoma. We always consider the decision for invasive diagnostics particularly carefully. If the patient does not want surgery, there is no reason for AVS; therefore, we can introduce a MRA. On the other hand, all diagnostic possibilities are offered to a patient who wishes to be surgically treated, has a high clinical probability of a unilateral form of the disease, and a significant possibility of cure (4), as in the clinical case presented below.

2 Case presentation

We present Mr Z.T., born in 1962, who was first referred to our endocrinology outpatient clinic in 2004 due to hypokalaemia. A severely low serum potassium 2.2 mmol/L (reference values 3.80–5.50 mmol/L) and very high BP 200/150 mm Hg was found in 2003 during his hospitalization at the Department of Traumatology. He has been treated for HTN since 2001 (nifedipine (Adalat OROS) 30 mg and irbesartan (Aprovel) 300 mg daily), and had no other chronic diseases. Both of his parents were hypertonics. His brother suffered a myocardial infarction at the age of 55.

A clinical exam in 2004 was uneventful, with the exception of an elevated BP (160/100 mm Hg). Laboratory test results showed a markedly low serum potassium (2.77 mmol/L), and after correcting for normokalemia we performed screening for PA that was positive (PAC 0.95 nmol/L; PRA 0.42 μg/L/h; ARR 2.26 nmol/L per μg/L/h). In addition to the already prescribed antihypertensive therapy, tablets of potassium citrate (Kalinor) were prescribed and further diagnostic testing was planned at our department. Upon admission the level of serum potassium still remained low (2.77 mmol/l), and PRA was completely inhibited (less than 0.15 μg/L/h). Since we

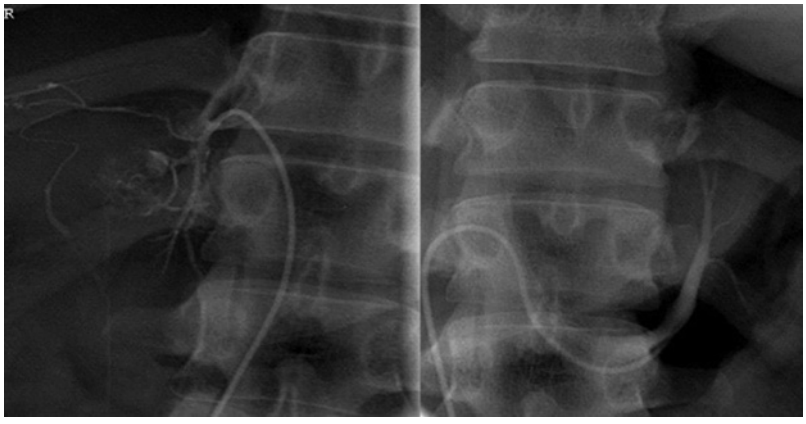

Figure 1: Angiogram during adrenal vein sampling.

have also found metabolic alkalosis typical for PA, we have introduced potassium chloride that contains only 6.7 mmol of potassium per tablet. In order to normalize serum potassium, the patient also required intensive replacement with an otherwise alkaline but significantly stronger Kalinor (40 mmol of potassium per tablet). A posture simulation test was carried out during which cortisol was reduced accordingly (287.8 nmol/L at 8 h and 173.5 nmol/L at 12 h), and aldosterone levels increased (0.78 nmol/L at 8 h and 1.04 nmol/L at 12 h), supposedly concordant with bilateral PA. We introduced an MRA - spironolactone (Aldactone), 50 mg daily. Confirmation test was not performed. Abdominal CT showed a 1 cm large tumor of the left adrenal gland resembling an adenoma. This was followed by an AVS, which was also supposed to be consistent with a bilateral hypersecretion of aldosterone (Table 1, Figure 1). Further administration of spironolactone (Aldactone) 50 mg was advised, as well as the remaining antihypertensive therapy (nifedipine (Adalat OROS) 30 mg and irbesartan (Aprovel) 150 mg daily).

A follow-up visit at the endocrinology outpatient clinic was not performed until 2014. At that time, the 51-year-old patient was referred to the clinic because of a gradual growth of the already known tumor of the left adrenal gland. In 2010, ultrasonography measurements were 23 × 24 mm, in 2011 it measured 23 × 25 mm, 25 × 28 mm in January 2013, and 28 × 29 mm in December 2013. The progressive growth, compared to the 2004 size, was also confirmed by the follow-up abdominal CT following an adrenal protocol, where a tumor of 26 × 29 × 29 mm tumor was now visible, an adenoma according to the CT criteria (Figure 2). For the past 3 to 4 years, the patient has observed that his blood pressure was more poorly regulated than in the past (average 155/105 mmHg, even up to 170/115 mmHg). His potassium level was monitored regularly every three months by his general practitioner and hypokalaemia was constantly present. The patient reported no major problems. Abdominal ultrasound scan in recent years also reported left-side neph-

Table 1: Results of the first adrenal vein sampling.

Place of sampling	Aldosterone (nmol/L)	Cortisol (nmol/L)
Right adrenal vein	58	> 30,000
Right adrenal vein through a microcatheter	33,4	> 30,000
Left adrenal vein	66,8	> 30,000
IVC	5.2	1113

Legend: IVC – inferior vena cava

rolithiasis and two gallbladder polyps. Only mild mitral and tricuspid regurgitation were seen echocardiographically. Chronic kidney disease of stage 1–2 was also found. Positive urinary catecholamines were among the control laboratory findings. Due to the known nephrolithiasis we also checked the calciotropic axis and found no deviations.

A hospitalization followed as an attempt to further evaluate the hormonal activity of the formation in the left adrenal gland. Urinary catecholamines were low normal this time, which excluded the possibility of a pheochromocytoma. Due to the patient's severe hypokalaemia it was difficult to withdraw spironolactone, normalize potassium by supplements and reliably confirm PA with saline infusion test (basal PAC 3.86 nmol/L, 3.52 nmol/L after 240 min). After carefully reviewing old medical records, we found that the patient was on spirolactone during the first AVS test, which is contraindicated, so the test was performed again while he was off the medication; unfortunately, it was technically unsuccessful due to the patient's complex vascular anatomy and lack of an adequate catheter. AVS was then repeated for the third time, this time successfully. Despite a biochemically pronounced PA, surprisingly, a unilateral PA was yet again not confirmed (Table 2), since the aldosterone/cortisol ratio between the left and right adrenal vein (LI) was only 2.7. We proceeded with MRA and prescribed eplerenone (Inspra).

In the beginning of 2015, about half a year after the last AVS, the patient once again expressed his wish for surgical treatment. Serum potassium and blood pressure were not well controlled despite the already very high dose of eplerenone (Inspra 2×100 mg) and combination antihypertensive therapy (nifedipine (Adalat OROS) 2×60 mg and irbesartan (Aprovel) 300 mg in the morning). We did not have the basis for surgical treatment apart from the slowly growing tumor of benign appearance, however, considering the long-lasting, difficult-to-manage form of PA, and despite three AVS that were unable to confirm a unilateral form of the disease, in September 2015, we suggested the patient should undergo a 11C-metomidate PET-CT in the United Kingdom. The result of this procedure was positive in terms of an aldosteronoma of the left adrenal gland (Figure 3). They also performed a 1 mg dexamethasone test (1-mg DMT) that did not show a complete suppression (cortisol 81 nmol/L, normally below 50 nmol/L). Autonomous cortisol secretion from the tumor was later also confirmed in our institution. In September 2016 the patient underwent a laparoscopic left adrenalectomy. He received glucocorticoid coverage during

Table 2: Results of the third adrenal vein sampling.

Place of sampling	Aldosterone (nmol/L)	Cortisol (nmol/L)	Aldosterone/cortisol ratio
Right adrenal vein	56.60	19010	0.00297
Left adrenal vein	213.50	26293	0.00812
IVC	10.80	1181	0.0091

Legend: IVC – inferior vena cava

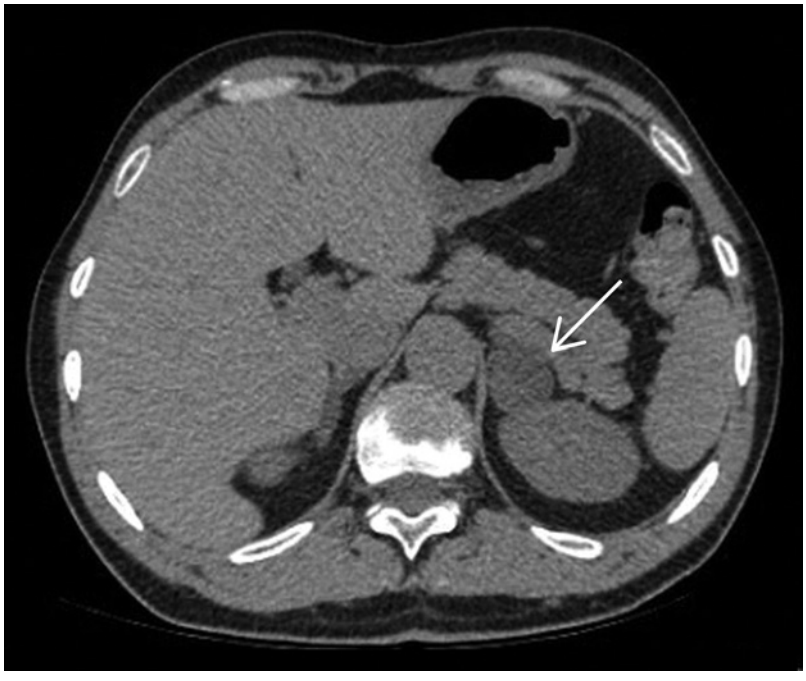

Figure 2: Left adrenal adenoma (arrow) on a CT image.

and after surgery. A postoperative insufficiency of the pituitary-adrenal axis was excluded. Pathohistological findings showed nodular hyperplasia of the adrenal cortex. The patient at first required potassium supplements immediately after the surgery, alongside high-dose hydrocortisone, and dual antihypertensive therapy (lacidipine (Lacipil) 6 mg in the morning, irbesartan (Aprovel) 300 mg in the morning), but during the hospitalization hydrocortisone and potassium replacement were discontinued. The BP started to decrease gradually with the introduced therapy.

During an outpatient follow-up examination in March 2017 the patient felt great. Serum potassium levels normalized and BP was well regulated only with telmisartan 40 mg daily. Hormonal check-up showed that primary aldosteronism was resolved (PAC 0.28 nmol/L; PRA 2.15 µg/L/h; ARR 0.13 nmol/l per µg/L/h).

3 Discussion

Hypertension as a result of mild hypervolemia remains the main feature of PA and is present in most patients, whereas hypokalaemia is believed to be most likely present only in a minority of PA patients (half of APA patients and one fifth of IHA patients) (5). In our case PA was easily considered because of a markedly elevated BP and persistent severe hypokalaemia. Furthermore, screening using ARR was also positive. Most patients with a positive ARR test require one or more confirmatory tests, such as a saline infusion test, in order to definitely demonstrate autonomous aldosterone secretion, as one third of patients with a positive ARR may in fact have essential hypertension (13).

This test was not carried out in 2004. Following the new recommendations for the diagnosis of PA, the presence of spontaneous hypokalaemia and completely inhibited PRA and PAC values > 550 pmol/L (5) are sufficient. All of these criteria were met in our patient, only PRA was initially not completely suppressed, most likely due to treatment with irbesartan (Aprovel).

In order to differentiate between the unilateral and bilateral forms of PA, a posture simulation test was carried out in 2004, which is no longer performed today due to its unreliability. The increase in angiotensin II in an upright position during the test does not only increase PAC physiologically and in patients with bilateral PA, but also in some patients with unilateral PA (5). A rise in PAC during the posture simulation test also occurred in our patient, which was supposed to speak in favour of a bilateral PA. Back in 2004, and especially 10 years later, it was clinically much more likely that this was a case of a unilateral PA. These patients have severe hyper-

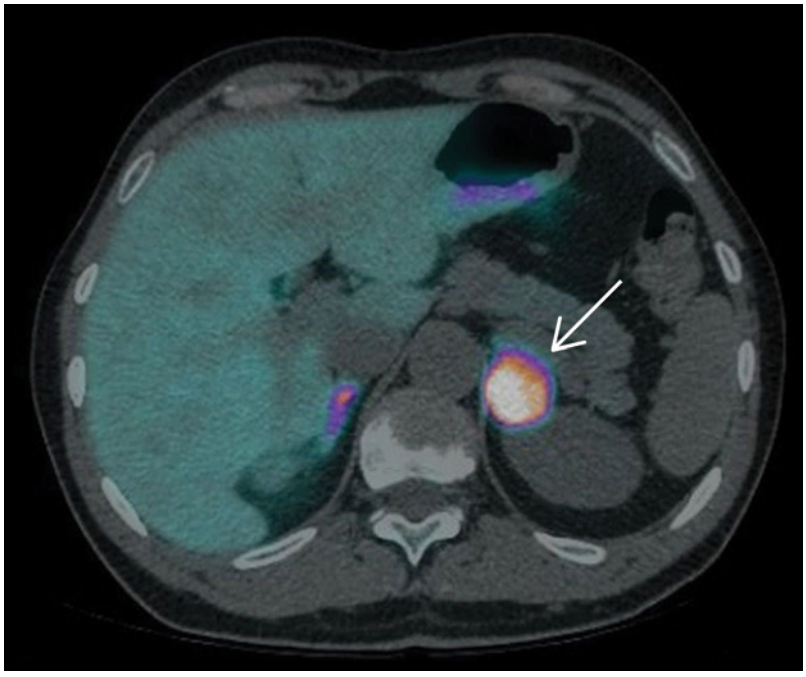

Figure 3: Left adrenal adenoma (arrow) on an 11-C-metomidate PET-CT image.

tension, high basal PAC (> 0.7 nmol/L) or high PAC after a saline infusion test (> 0.28 nmol/L), are younger than 50 years, and are more likely to be hypokalaemic than patients with bilateral PA (5).

Our patient underwent a CT of adrenal glands which showed a 1 cm large tumor in the left adrenal gland with an appearance of an adenoma. A CT and/or MRI are, however, not sufficiently precise methods for differentiating between unilateral and bilateral forms of the disease. In more than a third of the cases (37.8 %) of patients with PA imaging has shown a different result than AVS. A unilateral tumor can be seen when it is actually an IHA or even an APA on the other side, as well as bilaterally normal or abnormal glands, when it is in fact a unilateral APA (14). If a PA patient is a candidate for surgical treatment, AVS is usually required to confirm unilateral secretion of aldosterone (4). The only exception are patients under 35 years of age with spontaneous hypokalaemia, a marked excess of aldosterone, and a unilateral lesion with radiological characteristics of an adenoma, in which the CT scan results are in line with the AVS test results according to studies (4,5). Our patient was aged 42 years in 2004, so the AVS was indicated accordingly.

The diagnostic procedure was technically successful (SI above 5) and confirmed a bilateral excess secretion of aldosterone, so we continued to treat the patient with medications. Upon a thorough review of the results of the first AVS (Table 1) we can see that the final values of cortisol in the adrenal veins were not determined, so the calculation of LI and the interpretation of the test results were not even possible. Additionally, the patient was on spironolactone during AVS, which could stimulate the secretion of renin and, thus, the secretion of aldosterone from a healthy adrenal gland, which could affect the outcome of the test. It is impossible to determine if that was the case, since serum potassium was normal on the day AVS was performed and PRA value was not determined (10).

During follow-up ultrasound examinations in the following years a gradual growth of the change in the left adrenal gland was observed, and in 2014, the patient was again referred to our outpatient clinic. The follow-up CT confirmed the benign appearance of the tumor, as well as its significant growth in the 10 years since its diagnosis. The PA diagnosis was this time confirmed with a saline infusion test, which did not result in a sufficient reduction in PAC. According to highly conclusive clinical and laboratory findings, this type of testing as described above that required withdrawing of MRA for 4 weeks and at the same time resulted in having great difficulty in regulating markedly reduced potassium, was not even needed (5). Despite the growth of the tumor, we also decid-

ed to repeat the AVS because at its first attempt it was not performed correctly. The procedure was successful only in the second attempt. It is a known fact that AVS is a very demanding procedure. The key to success is an experienced and appropriately specialized interventional radiologist. The most difficult part is to locate and cannulate the shorter and smaller right adrenal vein, which is usually drained directly into the VCI (10). The average success rate of right-sided catheterization is only 74 % (4,5). The catheterization of the left adrenal vein is technically relatively simple. Since this vein usually merges with the lower phrenic vein before entering the VCI, there is an occurrence of dilution of the sample with blood from other tissues, so aldosterone levels should always be corrected to cortisol on both sides (5,10).

The blood sample from adrenal veins for cortisol assay in the first AVS was not diluted adequately; therefore the result of the procedure was inapplicable. The problem could be eliminated with AVS standardization, including a standardised AVS report (10).

It is surprising that even with the technically successful third AVS (SI > 5) we were unable to confirm the unilateral form of PA. It is possible that this was due to the simultaneous autonomic secretion of cortisol from the tumor, which was confirmed just before surgery. In fact, the value of cortisol in the left adrenal vein was significantly higher than on the right side, although it is usually the opposite due to the mixing of venous blood from the lower phrenic vein on the left.

A higher cortisol level may have significantly reduced the aldosterone/cortisol ratio in the left adrenal vein, which could also lower the LI value below the diagnostic threshold. In fact, the gradient of the aldosterone/cortisol ratio between the left and right adrenal vein, LI, was only 2.7. According to the size of the tumor, if it were an APA, we would expect a completely clear gradient in favour of the left side. Today, it is known that the autonomous secretion of cortisol from APA is much more common than we thought up until recently, so 1 mg DMT test should be performed in all patients who have a tumor of at least 1 cm (10,15). If the test is positive, it is necessary to use another hormone instead of cortisol to normalize aldosterone values during AVS, for example, metanephrine or androstenedione (16,17).

According to recent findings, a low ratio of aldosterone-to-cortisol between the adrenal vein on the tumor-free side and in VCI (contralateral suppression index (CSI)) may also help when deciding for an adrenalectomy (18). This is consistent with the result of the last AVS in our patient (CSI < 0.5).

Our patient had a marked form of PA with severe hypokalaemia and a distinctive tumor of the left adrenal gland, so maybe we could have opted for a laparoscopic left adrenalectomy only based on a CT scan and without AVS. A recent prospective randomized diagnostic study has shown that in exactly such patients with PA the success of the treatment outcome in regards to CT or AVS diagnostics does not differ in any way except in the price that is much higher if we also perform AVS (19). The design of this study and its findings were strongly criticized. An insufficient number of patients involved and, consequently, insufficient statistical power for any conclusions were highlighted in particular. The controversy has not yet been resolved (20).

Since our patient wanted surgical treatment due to unregulated blood pressure and persistent hypokalaemia despite combination antihypertensive

therapy and high dose of eplerenone, we confirmed a unilateral disease using 11C-metomidate PET-CT.

This functional-morphological test is non-invasive but difficult to access. In September 2015 across the whole Europe, it was only available in Addenbrooke's Hospital, Cambridge, UK. 11C-metomidate is a potent inhibitor of 11β-hydroxylase and aldosterone synthase, two steroidogenic enzymes in the adrenal cortex, and, therefore, a radiotracer selectively accumulating in an APA. Its short half-life (20 min) is problematic, so it must be prepared on-site (21,22). Burton and colleagues showed that the 11C-metomidate test with an optimal standardized uptake value (SUVmax) between tumor and surrounding adrenal tissue 1.25: 1 achieved 76 % sensitivity and 87 % specificity for APA confirmation. They concluded that the method is a sensitive and specific non-invasive alternative to AVS in PA diagnosis (23,24). The cost of this procedure is becoming comparable with the price of AVS, therefore, new diagnostic nuclear medical centres are being opened in Europe, and furthermore, there is on-going research on the possibilities of using other radiopharmaceuticals that are more specific and sensitive for APAs (21,22).

Hormonal findings after surgery have shown that PA was biochemically resolved, and the patient's condition has, in relation to the duration of the illness and family history of HTN, as expected clinically significantly improved, but was not completely cured (11,12).

4 Conclusion

The presented case demonstrates that a sound clinical judgment is of key importance even in complex diagnostic work-up. Despite the negative findings of AVS, which represents the gold standard for differentiation between unilateral and bilateral PA, we took into account the clinical and laboratory characteristics of the patient that spoke in favour of a unilateral illness, which we were able to confirm, and practically cure HTN using surgery.

The patient agrees with the publication of the article.

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