World Journal of Case Reports and Clinical Images

ISSN: 2835-1568; CODEN: USA

DOI: http://dx.doi.org/10.51521/WJCRCI.2025.e42.419

CASE REPORT

Unveiling Primary Aldosteronism in the Absence of Adrenal Morphological Abnormalities: A Case Report in a Hypertensive Female

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Received Date: 30-September-2025
Revised Date: 15-September -2025
Accepted Date: 20-October-2025
Published Date: 31-October-2025

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Citation:
Ikram Tahani, Yasmine Ouaddouh, Soumia Boulouiz, Zakaria Bazid, Noha El Ouafi, Nabila Ismaili (2025) Unveiling Primary Aldosteronism in the Absence of Adrenal Morphological Abnormalities: A Case Report in a Hypertensive Female. World J Case Rep Clin Imag. 2025 October; 4(2)1-8.

Abstract

Primary aldosteronism [PA] represents a well-recognized etiology of secondary hypertension, most commonly attributed to aldosterone-producing adenomas and bilateral adrenal hyperplasia, which together account for over 95% of documented cases. Less frequently, PA may arise from adrenal carcinoma or hereditary forms such as familial hyperaldosteronism. In recent years, however, an expanding subset of patients has been described in whom standard imaging fails to reveal discernible adrenal abnormalities, thereby complicating disease subtyping and therapeutic decision-making. Such atypical presentations pose considerable diagnostic challenges and often require advanced investigations to guide optimal management. Here, we report the case of a 45-year-old hypertensive woman with a history of migraine, whose adrenal MRI appeared unremarkable despite biochemical evidence strongly suggestive of PA.

Keywords: Primary aldosteronism, Adrenal imaging, Normal adrenal MRI, Secondary hypertension, Atypical presentation.

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1. Introduction:

Primary aldosteronism [PA] is the most common cause of secondary hypertension, affecting approximately 10% of the hypertensive population and up to 23% of patients with resistant hypertension [4], where an aldosterone to renin ratio [ARR] of greater than 23 is highly suggestive of PA [11]. The diagnosis of PA is often complicated by the presence of factors such as oral contraceptive use, which can lead to false positives in the ARR, a key diagnostic marker. Despite continuous advancements in cross-sectional imaging technologies, the diagnostic and lateralization capabilities of computed tomography [CT] and magnetic resonance imaging [MRI] remain limited. These imaging modalities may be particularly ineffective in detecting small adrenal adenomas, necessitating the use of additional lateralization techniques, such as adrenal vein sampling [AVS] [6]. In this paper, we will highlight the unique case of a 45-year-old female diagnosed with primary aldosteronism [PA], despite normal adrenal imaging findings, emphasizing the challenges in diagnosing PA and the importance of a comprehensive diagnostic approach.

2. Case Presentation:

We present the case of a female patient aged 45-year-old who initially presented to her physician at the age of 33 with uncontrolled, resistant hypertension, manifesting as helmet headaches accompanied by tinnitus. Despite the administration of six antihypertensive agents, including a calcium channel blocker [amlodipine], a renin-angiotensin-aldosterone system inhibitor [valsartan], a thiazide diuretic [hydrochlorothiazide], a mineralocorticoid receptor antagonist [spironolactone], a centrally acting antihypertensive [clonidine], and a beta-blocker [bisoprolol], her blood pressure remained poorly controlled, with only minimal improvement. The patient's body mass index [BMI] was 28, and there was no family history of hypertension. Notably, she had been on combined oral contraceptive therapy [estrogen and progesterone] since the age of 18. In light of these features, the patient was referred to our cardiology department for comprehensive evaluation of possible secondary hypertension.

Initial laboratory tests suggested Primary Aldosteronism [PA] through the measurement of plasma aldosterone concentration [PAC], plasma renin activity [PRA], and the calculation of the aldosterone-to-renin ratio [ARR]. The ARR was markedly elevated on two separate determinations, yielding values of 111 and 143, respectively [Table 1]. These tests were conducted under the appropriate conditions: the patient was not on spironolactone for 6 weeks, nor on ACE inhibitors or beta-blockers for 2 weeks prior to testing. She followed a normo-sodium diet of 6g/day, as recommended by the French Committee for Blood Pressure Control. At the time of testing, her blood pressure was below 180/110 mmHg. Additionally, a 24-hour urinary sodium excretion of 194 meq/L and a 24-hour urinary potassium excretion of 52 meq/L were recorded. The measurements were taken after the patient remained in a supine position for 2 hours, followed by standing after a one hour walk.

Table 1: Biological data from the two assays supporting the diagnosis of biologically primary hyperaldosteronism.

Parameter	First Lab	Second Lab	Normal Values
ARR (Aldosterone to Renin Ratio)	111	143	< 23
PAC (Plasma Aldosterone Concentration)	515 (Standing) / 313 (Lying)	880 (Standing) / 317 (Lying)	67–335 pg/ml (Standing) / 42–209 pg/ml (Lying)
PRA (Plasma Renin Activity)	4.5 (Standing) / 4.8 (Lying)	3.4 (Standing) / 6.1 (Lying)	5.1–34 pg/ml (Standing) / 9–62 pg/ml (Lying)
Serum Potassium Level	4.1	4.9	3.5–5.0 mmol/L
Serum Natriuresis	142	139	135–145 mmol/L
24h Natriuresis	Not available	194	100–200 mmol/24h
24h Kaliuresis	Not available	52	> 50 mmol/24h

During this period, the patient underwent dedicated adrenal imaging, which included a CT scan that demonstrated normal adrenal glands, with no evidence of nodules or hyperplasia. Surprisingly, an adrenal MRI performed two years

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ISSN: 2835-1568; CODEN: USA

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later showed the same normal results [Figures 1 and 2]. This MRI could not be conducted sooner due to the patient being lost to follow-up. During this period, she was prescribed spironolactone and nicardipine.

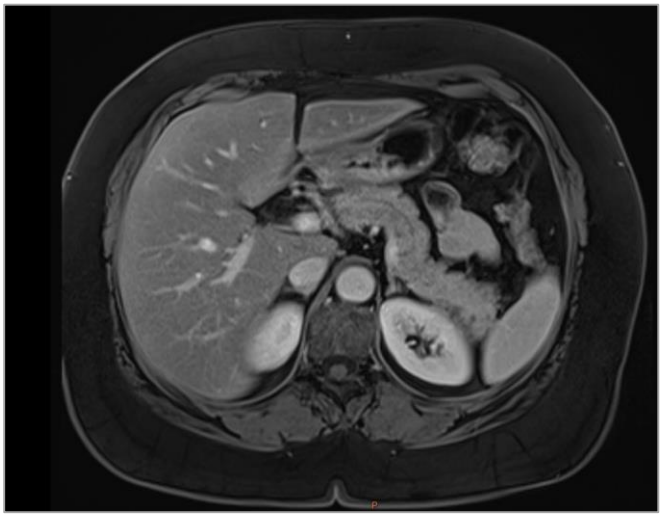

Figure 1: MRI axial T1-weighted image with contrast administration demonstrating normal-appearing adrenal glands.

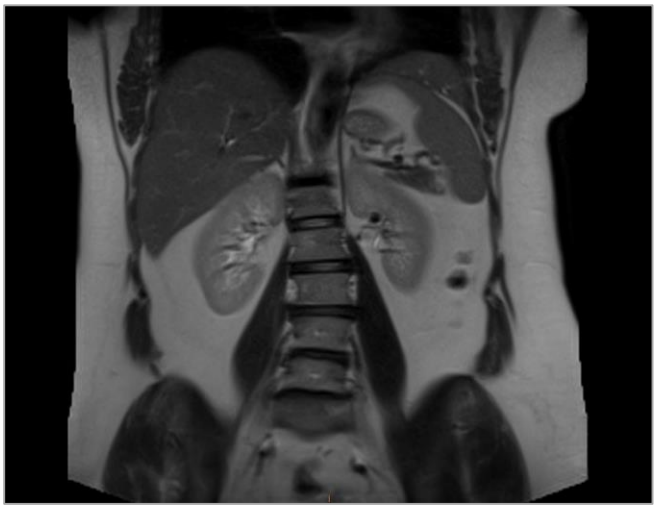

Figure 2: MRI coronal T2-weighted image without contrast administration demonstrating normal-appearing adrenal glands.

The determination of aldosterone secretion lateralization to one adrenal gland was not possible due to the lack of necessary diagnostic tools at our institution, such as adrenal venous sampling [AVS] and PET scan. Evaluation for other secondary causes of hypertension, including pheochromocytoma, Cushing's syndrome, renal artery stenosis, hyperthyroidism, and aortic coarctation, were undertaken, and these conditions were excluded. Given that the patient did not present any clinical symptoms indicative of secondary causes of hypertension [SAOs] and was not obese, these were not pursued further.

Her hypertension was both systolic and diastolic, sustained across the circadian cycle, with 24-hour ambulatory monitoring demonstrating the absence of a nocturnal dip. The maximum documented blood pressure was 230/110 mmHg. Target-organ involvement included stage I hypertensive retinopathy, classified according to Kirkendall, underscoring the necessity of strict blood pressure control.

The 12-lead Electrocardiography revealed electrical evidence of left ventricular hypertrophy [LVH], with an R-wave amplitude of 15 mm in lead DI, consistent with the Gubner index [Figure 3]. Transthoracic echocardiography showed a non-dilated left ventricle with mild concentric hypertrophy [wall thickness 13 mm] and preserved global and segmental systolic function, with an ejection fraction of 56%. The 24-hour urinary microalbumin-to-creatinine ratio remained within the normal range at 0.05.

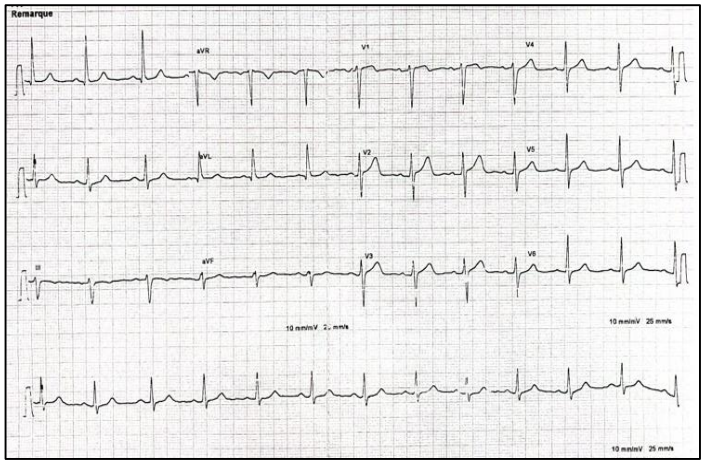

Figure 3: The 12-lead electrocardiogram showing electrical left ventricular hypertrophy (LVH), characterized by an R wave amplitude of 15 mm in lead DI (Gubner index)

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As subgrouping could not be performed in our patient, she was maintained on high-dose spironolactone [200 mg per day] in combination with nicardipine [10 mg per day], which resulted in good initial clinical progress and normalization of blood pressure measurements. However, at the age of 46, she developed chronic right-sided headaches with visual aura, suggestive of migraine. A cerebral CT scan was performed, which returned normal. Following this, our neurology colleagues-initiated treatment with pregabalin 150 mg per day, with a favorable clinical response.

3. Discussion:

Primary aldosteronism [PA], first described by Conn in 1954 [1], is now recognized as the most common form of secondary hypertension, with a prevalence of 6–20% among hypertensive patients [4,5]. Beyond blood pressure elevation, aldosterone excess exerts direct cardiovascular toxicity through oxidative stress, endothelial dysfunction, and vascular fibrosis, contributing to adverse outcomes independent of hypertension [3]. Despite guideline recommendations for systematic screening using renin and aldosterone measurements, implementation in routine practice remains inconsistent, underscoring the need for greater clinical awareness [5].

The actual current challenge in PA lies in subgrouping, as the therapeutic strategy depends on the specific subtype. Indeed, three subtypes have been described:

1. Aldosterone-producing adenoma [APA] is defined by concordant results between the unilateral adrenal nodule detected by CT or MRI and lateralized aldosterone production as assessed by AVS, which is finally pathologically proven [4].
2. Primary adrenal hyperplasia [PAH] is defined by normal, unilateral, or bilateral plump on CT, and lateralized aldosterone production as assessed by AVS [4].
3. Bilateral adrenal hyperplasia [BAH] was defined by normal or bilateral CT abnormalities and bilateral aldosterone secretion or unilateral aldosterone secretion on AVS that clinically is not improvement after adrenalectomy [4].

Computed tomography [CT] is the modality of choice for detecting aldosterone-producing adenomas [APA]. It is a fast, non-invasive, and easily accessible tool [6][7]. However, up to 20% of APAs have been reported to be smaller than 1 cm, and CT scans may miss these nodules [6][8]. In this context, the prevalence of primary aldosteronism with normal-appearing bilateral adrenals appears to be relatively low, accounting for no more than 20% of cases across various studies. Specifically, in a study conducted in Thailand involving 243 patients, 43 [18%] exhibited bilateral normal-appearing adrenals, while 200 [82%] presented with a unilateral normal-appearing adrenal [10].

Lateralization of aldosterone secretion can be achieved through three primary methods: metomidate positron emission tomography [PET], measurement of 18-oxocortisol, or, most commonly, adrenal vein sampling [AVS] [7]. AVS is considered the gold standard for differentiating between unilateral and bilateral aldosterone production, with sensitivity approaching 100% [9]. However, this procedure is invasive and technically challenging, particularly with right renal vein catheterization. AVS also requires prolonged fluoroscopy, which exposes the patient to significant radiation. Additionally, complications such as venous extravasation, hemorrhage, and adrenal vein thrombosis can occur. The success rate of AVS depends on the experience of the angiographer, with failure rates as high as 30% [6]. The procedure [AVS] can be skipped in patients with a single nodule bigger than 10 mm and younger than 35 years of age. In all other cases, if both the physician and patient are amenable to surgery, AVS should be performed [7]. For our patient, lateralization could not be

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achieved due to the unavailability of necessary tools in our hospital.

It is essential to consider alternative forms of primary hyperaldosteronism, particularly glucocorticoid-remediable aldosteronism [GRA]. In the present case, the absence of hypokalemia further suggests the need to exclude GRA, a rare form of familial hyperaldosteronism with an autosomal dominant inheritance pattern, often leading to hypertension in early childhood in up to 80% of cases [12]. GRA is named as such because it represents a form of primary aldosteronism that can be effectively managed or "remediated" through the administration of glucocorticoids. This condition arises due to a genetic mutation that results in the fusion of the aldosterone synthase gene with the 11β-hydroxylase gene. This fusion leads to the aberrant regulation of aldosterone production, whereby the adrenal glands become inappropriately responsive to adrenocorticotropic hormone [ACTH], which typically stimulates cortisol synthesis. The hallmark of GRA is that glucocorticoid treatment suppresses ACTH secretion, thereby reducing the excess production of aldosterone and alleviating the symptoms of the disorder [12]. Notably, hypokalemia is usually absent in GRA, and this diagnosis was ruled out in the present case, as the patient began exhibiting symptoms in her third decade of life and lacked a family history of the condition.

Migraine is a neurological disorder that is extremely common and disabling, characterized by a complex neurobiology, involving a series of central and peripheral nervous system areas and networks [5]. In the 1930s, Harold G. Wolff and colleagues, postulated the well-known vascular theory of migraine in which arterial dilation is the main causative process [5]. This hypothesis was later corroborated through the observation of arterial intracranial dilation using 3-Tesla [3T] magnetic resonance angiography. Primary aldosteronism [PA] is known to induce vessel dilation primarily through mineralocorticoid receptors by increasing the density of fibronectins and collagen, which contribute to excessive remodeling and enzymatic degradation of the extracellular matrix, resulting in the thinning of vessel walls [14]. Moreover, the presence of mineralocorticoid receptors [MR] in several central nervous system structures responsible for cognitive functions such as the hippocampus, amygdala, prefrontal cortex, and brain vasculature has been well-documented [15]. This may elucidate the potential link between migraine and PA, as evidenced in the case of our patient, who developed migraine symptoms during follow-up.

A significant issue with patients using oral contraception is the risk of false positives for primary aldosteronism [PA]. The results of the Reine Australian study highlight significantly higher rates of the aldosterone-to-renin ratio [ARR] in oral contraceptive [OC] users [235 patients] compared to non-users [251 patients] at 27 years of age [27.3% vs 21%], with no apparent relationship between ARR and blood pressure [20]. Our patient, who had been using oral contraceptive estrogen/progestin [Levonorgestrel/Ethinylestradiol] since the age of 18, discontinued the contraceptive several months prior to the second follow-up for primary hyperaldosteronism. Despite the discontinuation, her blood pressure remained elevated. Notably, the two check-ups performed showed markedly elevated aldosterone levels and an increased ARR, suggesting that these findings could not be attributed solely to the use of oral contraception.

In hypertensive patients diagnosed with primary aldosteronism who do not require surgical adrenal intervention, effective mineralocorticoid blockade is essential not only for controlling blood pressure but also for protecting against cardiovascular and cerebrovascular damage caused by aldosterone excess.

Spironolactone, the most commonly used mineralocorticoid receptor antagonist [MRA], has been shown to be more effective than eplerenone in controlling blood pressure. This was confirmed

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in a multicenter, randomized, double-blind, noninferiority study involving 141 patients, where response rates [defined as achieving a diastolic blood pressure <90 mm Hg or a reduction in diastolic blood pressure of 10 mm Hg from baseline] were significantly higher with spironolactone compared to eplerenone at all data collection points [4, 8, 12, and 16 weeks] [21]. These results can be explained by the lower binding affinity of eplerenone [approximately 20-fold weaker in vitro] and the inactivity of its metabolites. In contrast, spironolactone is frequently associated with adverse side effects, including gynecomastia, breast tenderness, menstrual abnormalities, and impotence, which are thought to result from its off-target agonist activity at the progesterone receptor and its antagonist activity at the androgen receptor. These side effects are less commonly observed with eplerenone [21]. Our patient, who was on 200 mg of spironolactone, experienced good blood pressure control without any side effects. Eplerenone was not considered as a treatment option due to its unavailability in our country.

4. Conclusion:

Morphologically normal-appearing adrenal glands are less common but can still be a source of aldosterone production. This pattern necessitates further investigation, particularly through adrenal venous sampling [AVS] for lesion lateralization. However, AVS carries multiple risks and potential failures. In cases where lateralization cannot be achieved, medical therapy using mineralocorticoid receptor [MR] antagonists, such as spironolactone, appears to be effective and safe. Regular clinical and potentially radiological monitoring of these patients would be beneficial for better management and optimal outcomes.

Disclosures Summary:

Acknowledgments: We thank all study team members for implementation and cooperation in this study, and we are also grateful for the Laboratory of Epidemiology, Clinical Research and Public Health of Faculty of Medicine and Pharmacy, Oujda, Morocco.

Conflict of Interest Statement: In compliance with the ICMJE uniform disclosure form, all authors declare that no financial support was received from any organization for the submitted work, and have no conflict of interest.

Patients Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Abbreviations: Primary aldosteronism, adrenal venous sampling [AVS], aldosterone to renin ratio [ARR], secondary hypertension.

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ISSN: 2835-1568; CODEN: USA

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Request PDF [Internet]. [cited 9 Feb 2025]. Available from: https://www.researchgate.net/publication/51537997_Spironolactone_is_More_Effective_Than_Eplerenone_at_Lowering_Blood_Pressure_in_Patients_With_Primary_Aldosteronism