CLINICAL NEPHROLOGY TEACHING CASE

Approach to the Patient With Hypertension, Unexplained Hypokalemia, and Metabolic Alkalosis

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• **We present a patient with hypertension and hypokalemia secondary to an aldosterone-producing adenoma that was renin responsive (APARR). We discussed the sequential approach to the diagnosis of the different subtypes of primary aldosteronism and confirmed the presence of an APARR. The most common cause of primary aldosteronism is an aldosteronoma; functionally, these adenomas respond poorly to angiotensin II but show a brisk response to adrenocorticotropin hormone. They have a pattern of aldosterone level that declines in parallel with cortisol levels. Our patient had an APARR, with an increase of aldosterone in the upright posture. The unusual physiologic response, incidence, and clinical characteristics of APARR are reviewed.**

INDEX WORDS: Hypertension; hypokalemia; metabolic alkalosis; hyperaldosteronism; glucocorticoid remediable aldosteronism.

OF ALL PATIENTS with high blood pressure presenting to the primary care physician, greater than 90% have primary hypertension; the cause of hypertension is not readily definable. The association of hypertension, unexplained hypokalemia, and often metabolic alkalosis should prompt the search for secondary hypertension.[1] When hypokalemia is due to inappropriate kaliuresis (urinary losses >25 to 30 mEq/d), the yield of finding potentially remediable forms of hypertension, such as primary aldosteronism, can be 75%.[2] It is not necessary to screen every hypertensive patient with hypokalemic metabolic alkalosis for primary mineralocorticoid overproduction if the patient is receiving high doses of diuretic. However, when serum potassium is less than 3 mEq/L in the steady-state of a patient taking recommended doses of diuretics, work-up is recommended.[3]

We present a patient with hypertension and unexplained hypokalemic metabolic alkalosis who was found to have an aldosterone-producing adenoma (APA). The unusual characteristic of this patient is that the APA was renin responsive (APARR). In addition, we review the work-up of patients presenting with hypertension and hypokalemic alkalosis.

CASE REPORT

A 49-year-old black man from Jamaica first presented to us in 1986, with a blood pressure of 210/120 mm Hg and a left cerebrovascular accident. In December 1988, the patient was seen again in the emergency department; he had a blood pressure of 210/130 mm Hg and a funduscopic examination with arteriovenous nicking and silver wiring. At that time, the patient was taking labetalol, 200 mg twice a day; triamterene and hydrochlorothiazide (Maxzide), 37.5/25 mg once a day; and dipyridamole (Persantine), 50 mg three times a day. The electrocardiogram showed left ventricular hypertrophy, and laboratory data were sodium, 138 mEq/L; potassium, 2.9 mEq/L; bicarbonate, 37 mEq/L; blood urea nitrogen, 22 mg/dL; and creatinine, 1.6 mg/dL. Maxzide was stopped, and nifedipine and potassium chloride were added to his regimen.

Three months later, while patient was taking potassium chloride, 50 mEq three times a day; labetalol, 200 mg twice a day; and nifedipine, 20 mg three times a day, the repeated chemistry showed persistent hypokalemic metabolic alkalosis. A 24-hour urine specimen showed urinary potassium, 58 mEq/d, and urinary sodium, 89 mEq/d. The patient had a plasma aldosterone level of 33 ng/dL and peripheral plasma renin activity (PRA) of 0.7 ng/mL/h, with an aldosterone/PRA ratio of 47. Urinary aldosterone excretion was 21 μg/24 hours (normal value, 1.6 to 6.2 μg/24 hours).

In December 1989, a computed tomography (CT) scan of the abdomen showed prominent right and left adrenals. The patient was placed on a regular sodium diet, and a postural test showed a postural-dependent aldosterone increase. The supine hormone levels were found to be 55 ng/dL for aldosterone and 12.5 μg/dL for cortisol with a PRA of 0.44 ng/mL/h; the upright levels were found to be 198 ng/dL for aldosterone and 12.7 μg/dL for cortisol with a PRA 0.22 ng/mL/h. In June 1990, iodine-131 cholesterol scan showed asymmetric activity, left more than right. In July 1990,

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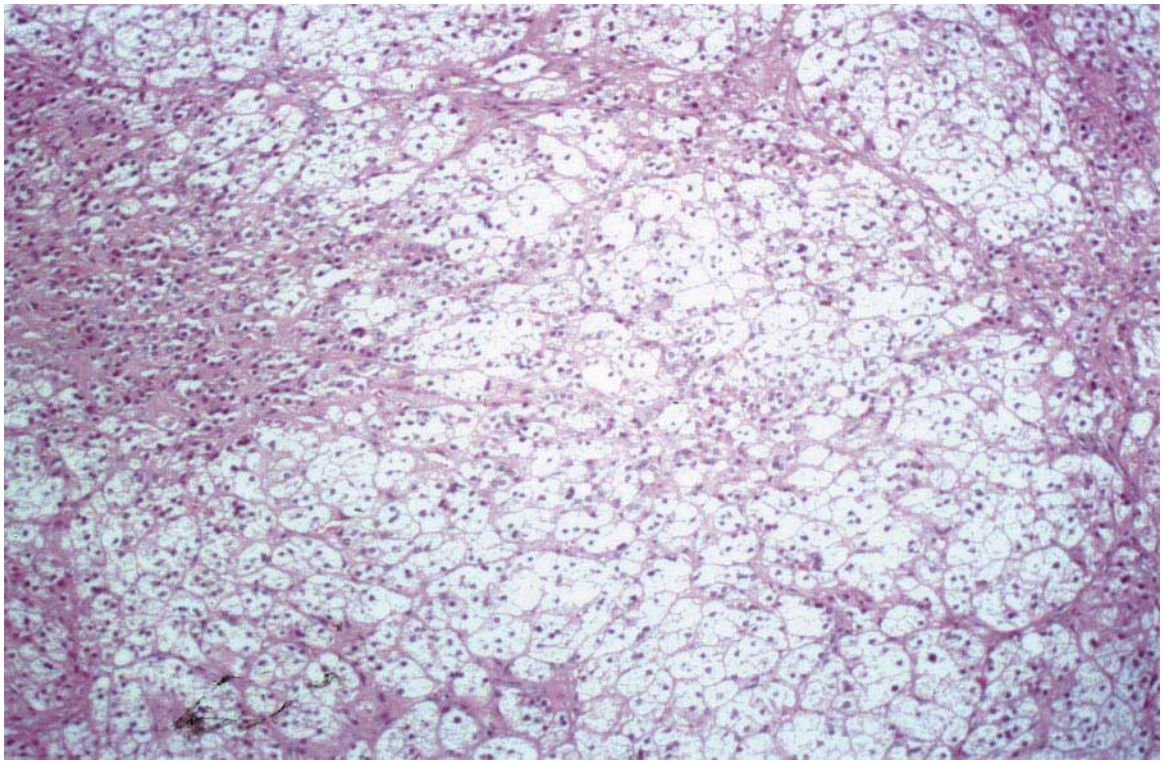

Fig 1. Microscopy of left adrenal gland. Notice two different cell populations: lipid-laden clear cells and compact cells of adrenal cortex, compatible with adenoma.

adrenal veins sampling of aldosterone/cortisol was performed and showed a lateralized aldosterone secretion to the left (left adrenal vein aldosterone [A], 18,000 ng/dL; cortisol [C], 120 μg/dL; and A/C ratio, 150; right adrenal vein aldosterone, 33 ng/dL; cortisol, 34 μg/dL; and A/C ratio, 0.97; and inferior vena cava aldosterone, 107 ng/dL; cortisol, 30.8 μg/dL; and A/C ratio, 3.47).

The patient underwent a left adrenalectomy, and a 1.2 $\times$ 1.2 $\times$ 0.5 cm adenoma was found (Fig 1). The hypokalemic metabolic alkalosis subsequently improved without the need of potassium replacement. Also, the patient's blood pressure was controlled easily during the ensuing weeks. During his last visit in January 1999, the patient had a blood pressure of 130/70 mm Hg on nifedipine XL, 60 mg/d.

DISCUSSION

Approach to the Patient With Hypertension and Hypokalemic Alkalosis Resulting From Primary Aldosteronism

The initial approach to patients such as ours presenting with hypertension, hypokalemia, and metabolic alkalosis consists of a sequential clinical evaluation including history and physical examination as well as preliminary laboratory data. The history should include inquiring about medications such as diuretics, β_2-agonists, and laxatives; the potential use of European black licorice needs to be considered. In the United States, glycyrrhizic acid, the active agent of licorice, may be ingested in capsules from health food stores and in chewing tobacco. The medication carbenoxolone, used to treat peptic ulcer disease in other countries, may cause hypertension and hypokalemia.

The second step is to confirm inappropriate kaliuresis when the patient has been off non–potassium-sparing diuretics. This finding suggests excessive mineralocorticoid production and should be established first, before doing imaging studies of the adrenal gland, because nonfunctioning adrenal mass lesions are relatively common in the general population.

The next step is to measure plasma aldosterone and PRA levels. Ideally the patient should be off diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, and β-blockers. The results of these measurements help to group these patients into three categories (Fig 2). First, in the high aldosterone–high PRA category, secondary aldo-

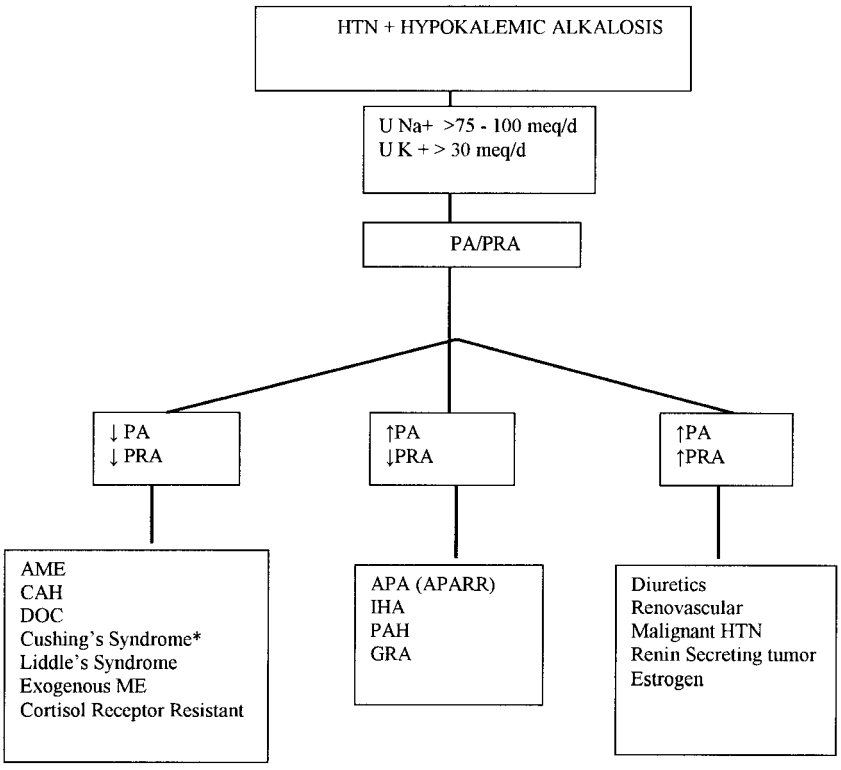

Fig 2. Differential diagnosis of hypertension and hypokalemic alkalosis. Abbreviations: HTN, hypertension; U Na^+, urinary sodium; UK^+, urinary potassium; PA, plasma aldosterone; PRA, plasma renin activity; AME, apparent mineralocorticoid excess; CAH, congenital adrenal hyperplasia; DOC, deoxycorticosterone-secreting tumor; ME, mineralocorticoid; APA, aldosterone-producing adenoma; APARR, aldosterone-producing adenoma, renin responsive; IHA, idiopathic hyperaldosteronism; PAH, primary adrenal hyperplasia; GRA, glucocorticoid remediable aldosteronism. *Ectopic adrenocorticotropin hormone-producing tumors.

steronism, such as surreptitious intake of diuretics, renovascular hypertension, and malignant hypertension, should be considered; estrogen-induced hypertension and renin-producing tumors also can produce secondary aldosteronism. In the low aldosterone–low peripheral PRA category, the main diagnoses to consider are exogenous mineralocorticoid intake, Cushing's syndrome, apparent mineralocorticoid excess, congenital adrenal hyperplasia, Liddle's syndrome, and deoxycorticosterone-producing tumor. In the high aldosterone–low peripheral PRA category, the main diagnosis is primary aldosteronism.

In our patient, the presence of hypertension, hypokalemia resulting from inappropriate kaliuresis, suppressed peripheral PRA, and increased aldosterone excretion was consistent with primary aldosteronism, which first was described by Conn[6] in a patient with an APA in 1955. Although hypokalemia is a hallmark in this syndrome, normokalemia does not exclude primary aldosteronism. Several studies have shown that 7% to 38% of patients with primary aldosteronism[4,5] have baseline serum levels of potassium in the normal range, which may be due in part to a low sodium intake when the test is performed, limiting kaliuresis. Patients with glucocorticoid-remediable aldosteronism are usually mildly hypokalemic or normokalemic. The prevalence of primary aldosteronism in an unselected hypertensive population is approximately 2%.[5] Primary aldosteronism can have a prevalence of 20% in a highly selected referral population, however.[6]

In screening for primary aldosteronism, a plasma aldosterone/peripheral PRA ratio greater than 30 and a plasma aldosterone value greater than 20 ng/dL provide a sensitivity of 90% and specificity of 91%.[7,8] The use of β-blockers, spironolactone, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers is not recommended during screening for primary aldosteronism because of their intricate interactions with the renin-angiotensin system. If antihypertensive medication is needed, α-blockers and calcium channel blockers have the least interference while measuring aldosterone levels and PRA. Aldosterone overproduction can be documented easily by finding a high urinary aldosterone excretion in a 24-hour urine collection.[4,9] The 24-hour urinary sodium excretion should exceed 75 to 100 mEq to document adequate sodium repletion. Urinary aldosterone excretion

of greater than 12 μg/24 hours in this setting is consistent with hyperaldosteronism.[10]

Types of Primary Aldosteronism

Several subtypes of primary aldosteronism have been described in the literature. APA or aldosteronoma is the most common cause of primary aldosteronism, accounting for approximately 65% of the cases. Most of those tumors are corticotropin responsive, and in rare instances APARR is present. APA characteristically responds more to adrenocorticotropic hormone (ACTH) than to angiotensin II; aldosterone levels in blood collected at 8 A.M. from supine patients do not rise subsequently to levels greater than 33% above baseline by noon (upright posture) and often exhibit an anomalous fall coincident with the diurnal decrease of ACTH. Our patient had an APARR and responded physiologically differently compared with the most common APA. During the postural test, the aldosterone level increased almost four times the basal level with the upright posture. Review of literature by others showed that APARR is a rare type of primary aldosteronism.[11] The four young patients reported presented with mild hypokalemia and lower urinary and plasma aldosterone levels compared with patients with aldosteronomas. These tumors are uncommon subtypes of APA that are angiotensin II responsive (postural responsive), and the aldosterone concentration does not parallel the circadian rhythm of the ACTH concentration. APA can de divided into two main subtypes based on morphology and biochemical behavior; most are corticotropin responsive as explained earlier and morphologically are composed predominantly of fasciculate-like cells. The other subtype (APARR) is composed predominantly of glomerulosa-like cells and is responsive to angiotensin II. The renin gene often is overexpressed in the second variety of adenoma and in surrounding nontumorous cortex.

Aldosteronomas occur more commonly in women than in men; occur at a younger age ($<$50 years); and have more severe hypertension, profound hypokalemia ($<$3 mEq/L), and higher plasma ($>$20 ng/dL) and urinary ($>$30 μg/24 h) levels of aldosterone than idiopathic hyperaldosteronism. The latter, which is associated with bilateral micronodular or macronodular hyperplasia, constitutes 20% to 30% of the cases of primary aldosteronism. Idiopathic hyperaldosteronism is more common in men and occurs at an older age than APA. Primary adrenal hyperplasia, aldosterone-producing adrenocortical carcinoma, and ectopic aldosterone-producing embryonic rest neoplasm account for less than 5% of cases.[4-11] Familial hyperaldosteronism type I or glucocorticoid remediable aldosteronism is a rare familial form of hyperaldosteronism.

The greatest challenge after making the diagnosis of primary aldosteronism is to differentiate among the several subtypes of primary aldosteronism (Fig 3). This differentiation is important because unilateral adrenalectomy in patients with APA or primary adrenal hyperplasia results in normalization of hypokalemia and improvement of hypertension in approximately 60% to 70% of cases. In idiopathic hyperaldosteronism and glucocorticoid-remediable aldosteronism, adrenalectomy seldom corrects the hypertension. The evaluation should include a high-resolution CT scan of the adrenals and measurement of 18-OH-corticosterone or urinary 18-OH-cortisol levels.

Among the localizing techniques, adrenal venous blood sampling and CT scanning are the most popular ones with accuracy of 95% and 73% (Table 1). High-resolution CT scanning can detect most aldosteronomas except those that are very small. As mentioned before, the appearance of a nonfunctional adrenocortical adenoma or incidentaloma discovered on a CT scan occasionally can cause confusion regarding the diagnosis of APA. Incidentalomas are seen in a great proportion of people with and without hypertension.[10]

When a solitary unilateral functional macroadenoma ($>$1 cm) and a normal contralateral adrenal morphology are found on CT scan in a patient with primary aldosteronism and increased plasma 18-OH-corticosterone or urinary 18-OH-cortisol, unilateral adrenalectomy is a reasonable therapeutic option. In many cases, however, CT scan reveals normal-appearing adrenals, minimal unilateral adrenal gland thickening, unilateral microadenomas ($<$1 cm), or bilateral macroadenomas ($>$1 cm). Localization studies, such as adrenal vein sampling, should be performed (Fig 3).

Before localization studies, glucocorticoid-remediable aldosteronism should be excluded. These patients have atypical lesions or no lesions by CT scan and increased 18-OH-corticosterone

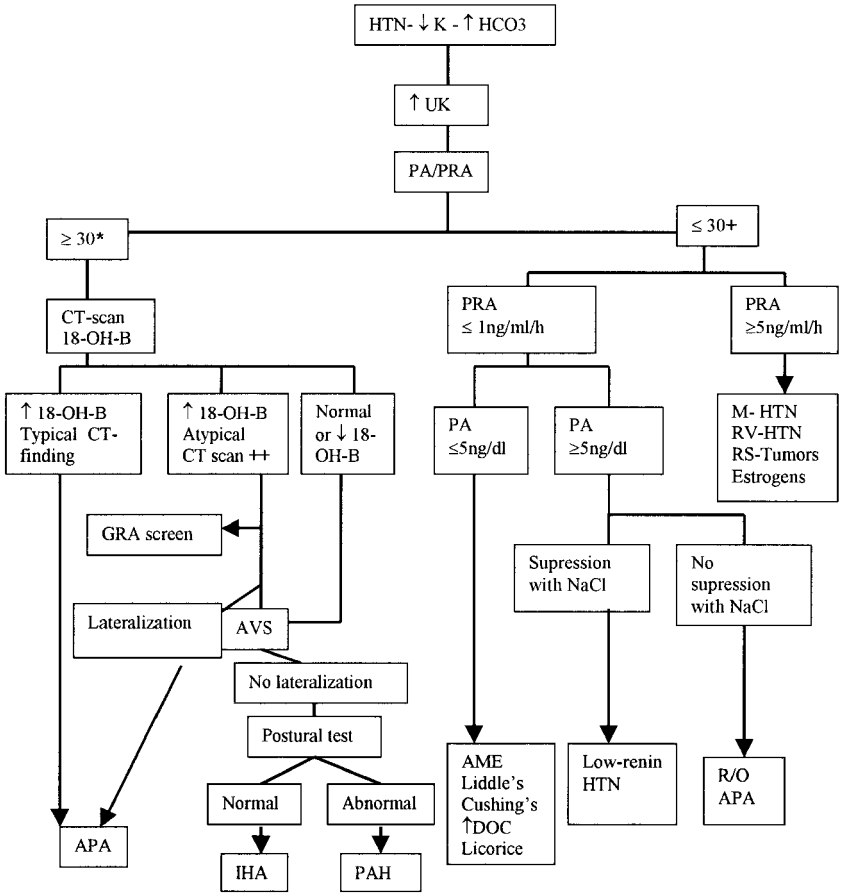

Fig 3. Work-up of hypertension and hypokalemic metabolic alkalosis. Abbreviations: HTN, hypertension; ↑UK, increased urinary potassium; PA/PRA, plasma aldosterone/plasma renin activity; 18-OH-B, 18-hydroxycorticosterone; GRA, glucocorticoid remediable aldosteronism; AVS, adrenal venous sampling; APA, aldosterone-producing adenoma; IHA, idiopathic hyperaldosteronism; PAH, primary adrenal hyperplasia; M-HTN, malignant hypertension; RV-HTN, renovascular hypertension; RS-Tumor, renin-secreting tumors; AME, apparent mineralocorticoid excess; Cushing's syndrome (ectopic ACTH-producing tumors); ↑DOC, increased deoxycorticosterone; low-renin HTN, low-renin hypertension. (*) PA, >20 ng/dL. (+) PA, <20 ng/dL. (++) Bilateral lesions, <1 cm bilateral lesion, >1 cm atypical.

or 18-OH-cortisol production. Glucocorticoid-remediable aldosteronism is an autosomal dominant disorder and results from the expression of a chimeric gene that encodes two enzymes, 11β-hydroxylase and aldosterone synthase in the outer zone of the adrenal cortex. In the zona glomerulosa, the expression of this chimeric gene leads to aldosterone production, which is regulated by adrenocorticotropin, rather than by angiotensin II. Consequently, plasma aldosterone fails to rise normally or falls during upright posture after overnight recumbency or during a midmorning angiotensin II infusion.[13] Glucocorticoid-remediable aldosteronism is associated with variable degrees of hyperaldosteronism, high levels of hybrid steroids (18-hydroxycortisol and 18-oxocortisol), and suppression with exogenous glucocorticoid.

A sampling of the adrenal venous blood, preferably with corticotropin stimulation[4,5] for measurement of aldosterone and cortisol, is the best method for localization of adenomas, provided that both adrenal veins can be catheterized successfully.[4,9] For adrenal venous sampling, an infusion of 50 μg/h of cosyntropin is initiated 30 minutes before adrenal vein catheterization and continued throughout the procedure to minimize stress-induced fluctuations in aldosterone secretion. The adrenal veins are catheterized through the percutaneous femoral venous approach. Blood is obtained from adrenal veins and the inferior vena cava below the renal veins and assayed for aldosterone and cortisol concentrations. Proper catheter placement should be confirmed by laboratory analyses of the blood samples showing higher concentrations of cortisol in the adrenal vein as compared with the inferior vena cava. Usually the ratio of ipsilateral to contralateral aldosterone concentrations in patients with APA is greater than 10:1.[12] In a review of 65 patients with primary aldosteronism at the Mayo Clinic from 1990 to late 1997,[13] most patients with a unilateral source of aldosterone had cortisol-corrected lateralization ratios (A/C) greater than 4.0. Ratios greater than 3.0 and less than 4.0 represented an overlap zone. Ratios of 3.0 or less

Table 1. Diagnostic Accuracy of Localization Studies Used in Patients With Surgically Proven Aldosterone-Producing Adenoma

Procedure	Total Tested (n)	Accuracy (%)*
Adrenal venous sampling†	384	95
Postural test	246	85
CT scan‡	313	73
Iodocholesterol scintigraphy	308	72
Adrenal venography	412	66

Abbreviation: CT, computed tomography.

* Accuracy is the sum of true positive and true negative results divided by total number.

† Adrenal venous sampling of both adrenal venous blood/aldosterone ratios $>$ 10:1 (with adrenocorticotropic hormone stimulation).

‡ CT should be used only after a clinical suspicion of primary aldosteronism owing to $\pm$10% prevalence of nonfunctional adrenal adenomas (autopsy 3-cm diameter highly suspicious of cancer).

were consistent with bilateral aldosterone secretion. Adrenal nuclear scanning with NP-59 (iodine-131 iodocholesterol) can be used to localize lesions if adrenal venous sampling is not feasible, although its accuracy is poor (Table 1). In patients who do not lateralize on adrenal venous sampling, a postural stimulation test may help separate patients with primary adrenal hyperplasia from patients with idiopathic hyperaldosteronism. The latter exhibit a postural increase in aldosterone of at least 33%, whereas in those with primary adrenal hyperplasia, aldosterone levels do not increase.

We have presented a patient with hypertension and hypokalemic alkalosis secondary to an APARR and reviewed the sequential approach to the diagnosis. The histologic specimen and response to surgical removal confirmed the presence of an APARR.

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