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NEDOUMICE U DIJAGNOSTICI PRIMARNOG ALDOSTERONIZMA

Sažetak: Aldosteron je mineralokortikoidni hormon poreklom iz glomerularne zone kore nadbubrežne žlezde. Njegov glavni mehanizam dejstva je reapsorpcija natrijuma, uz sekreciju jona kalijuma i vodonika, i predstavlja poslednji hormonski signal renin-angiotenzin-aldosteron sistema koji učestvuje u regulaciji cirkulišućeg volumena i sistemskog vaskularnog otpora. Hipokalijemija i hipertenzija su dva pokazatelja koja upućuju na razmišljanje u pravcu dijagnoze hiperaldosteronizma. Prikazali smo slučaj pacijenta kod kojeg je dijagnoza hipertenzije postavljena u njegovoj 30. godini. Prvi put je hipokalijemija registrovana u njegovoj 59. godini, 2023. godine (3,1 mmol/L). Analizirani *RAAS* markeri ukazali su da je ALDO/PRA odnos bio povišen. Kompjuterizovanom tomografijom dokazana je promena na desnoj nadbubrežnoj žlezdi veličine 9 mm. S obzirom na to da su bazne vrednosti aldosterona bile u opsegu za zdravu populaciju, uz suprimovanu vrednost plazma reninske aktivnosti u jednom uzorku, postavljena je sumnja na primarni aldosteronizam. Shodno tome, bilo je neophodno uraditi potvrdne supresione testove u cilju definisanja dijagnoze.

Ključne reči: sekundarne hipertenzije, aldosteronizam, hipokalijemija

Uvod:

Aldosteron je hormon kore nadbubrežne žlezde i predstavlja deo kompleksnog renin-angiotenzin-aldosteron sistema (*RAAS*) (1). U fiziološkim uslovima ovaj hormon reguliše elektrolitni status, tako što povećava reapsorpciju natrijuma, uz povlačenje vode za sobom, a sekretuje jone kalijuma (2). Jedan od mogućih razloga povećane

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produkcije aldosterona može biti patologija nadbubrežnih žlezda. Pored *RAAS*-a, postoje regulatorni mehanizmi koji su manjeg uticaja, poput adrenokortikotropnog hormona (*ACTH*), atrijalnog natriuretskog peptida (*ANP*) ili dopamina. Najveći broj pacijenata ima primarnu-esencijalnu hipertenziju, a 5 do 10% slučajeva može da ima sekundarnu, endokrinu hipertenziju, uključujući aldosteronizam, *Cushing*-ov sindrom ili oboljenje štitaste žlezde (3). Najčešći uzroci primarnog aldosteronizma su aldosteron produkujući adenom (*APA*), bilateralna adrenalna hiperplazija (*IHA*), a ređe su familijarne forme bolesti (4).

Prikaz slučaja:

Kod pacijenta muškog pola, starog 60 godina, postavljena je dijagnoza povišenog krvnog pritiska postavljena u njegovoj 30. godini života, dok je prvi put hipokalijemija (K: 3,1mmol/L) registrovana u 59. godini, koja se održava i po prekidu terapije diuretikom. Nefrološkom evaluacijom isključena je stenoza renalnih arterija. U ambulantnim uslovima analizirana je *RAAS* osovina, koja je ukazala na suprimovanu plazma reninsku aktivnost (0,7 μIU/mL; ref. vrednosti 2,8–39,9), uz neadekvatnu vrednost aldosterona, u opsegu za zdrave osobe (19,3 ng/dL), a odnos ALDO/PRA je granično povišen (*ARR*=27).

Tokom hospitalizacije na Klinici za endokrinologiju, dijabetes i bolesti metabolizma UKCS učinjena su ispitivanja u pravcu primarnog aldosteronizma. Kompjuterizovanom tomografijom je dokazana mala promena na desnoj nadbubrežnoj žlezdi veličine 9mm, a endokrinološkim funkcionalnim testovima isključena je autonomna kortizolska sekrecija i kateholaminski eksces. Na aldosteron neutralnoj terapiji registrovane su ponovo vrednosti aldosterona u referentnom opsegu za zdravu populaciju uz suprimovanu PRA u jednom uzorku (ALDO 345,5...254,4, PRA <0,3...5), zbog čega nismo mogli da isključimo dijagnozu primarnog aldosteronizma. Shodno tome, bilo je neophodno uraditi potvrdne supresione testove u cilju definisanja dijagnoze (Tabela 1, 2).

Tabela 1. Kaptoprilski test

Katroprilski test		
	ALDO ng/dL	PRA ng/mL/h
0 min	30	<0,3
120 min	15,44	0,48

Tabela 2. Infuzioni test

Infuzioni test		
	ALDO ng/dL	PRA ng/mL/h
0 min	21,83	0,35
30 min	13,59	1,70
60 min	18,46	<0,3
120 min	11,66	<0,3
240 min	10,39	1,1

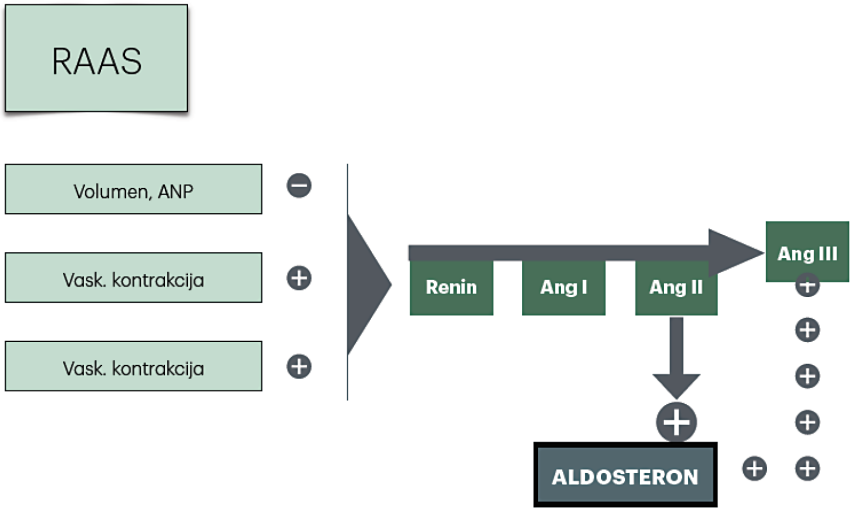
Ranije je registrovana atrijalna fibrilacija, koja je sanirana radiofrekventnom ablacijom. U 2023. g. imao je infarkt miokarda, kada su implantirana dva stenta. Ultrazvukom srca opisana je hipokinezija do akinezija bazalnog segmenta septuma i bazalnog segmenta inferoposteriornog zida (EF 60%). Porodična anamneza nije opterećena za ranu hipertenziju i kardiocerebrovaskularne događaje. Bivši pušač.

Diskusija:

Mineralokortikoidni hormon aldosteron je zadužen za održavanje cirkulišućeg volumena i serumskih koncentracija kalijuma, koji povratnom spregom regulišu lučenje aldosterona iz glomerularne zone kore nadbubrežne žlezde (Shema 1). Inhibitori aldosterona su ANP i lokalno dopamin, dok je aktivacija sinteze renina pod uticajem sniženog cirkulišućeg volumena i beta-adrenergičke stimulacije simpatikusa (5). Povišene vrednosti kalijuma inhibiraju sintezu renina, dok direktno pojačavaju sintezu aldosterona, što objašnjava činjenicu da *RAAS* predstavlja zaštitni kompenzatorni mehanizam od hiperkalijemije. Nasuprot tome, hipokalijemija smanjuje sintezu aldosterona, a diuretici koji favorizuju gubitak kalijuma utiču na koncentracije renina i aldosterona u plazmi. Renin se konvertuje u angiotenzinogen, a zatim u angiotenzin I, dok pod uticajem angiotenzin konvertujućeg enzima (ACE) pretvara angiotenzin II koji stimuliše aldosteron.

Finalni produkt angiotenzina II se metaboliše u jetri u angiotenzin III, heptapeptid koji takođe stimuliše lučenje aldosterona (6). Značajnu ulogu imaju prostaglandini I2 i E2, a dokazano je i da metoklopramid povećava lučenje aldosterona.

Shema 1. *RAAS*



Dve stvari koje navode lekare da razmišljaju u pravcu aldosteronizma su: 1. hipertenzija, naročito nastala u mlađem životnom dobu; 2. hipokalijemija. Prediktivna vrednost prisustva obe komponente je 50% (7). U ranijim godinama života primarni aldosteronizam može da bude asimptomatski. Pacijenti se uglavnom žale na glavobolju, crvenilo lica, zujanje u ušima, međutim, kod dugo nekontrolisane hipertenzije može doći do slabljenja vida, poremećaja svesti i hipertenzivne encefalopatije. Hipokalijemija može da dovede do umora, slabosti, opstipacije, poremećaja srčanog ritma, ali oko 60% osoba sa *PA* je normokalijemično (8). Shodno tome, od izuzetnog značaja je da se ovaj klinički entitet prepozna s obzirom na mnogobrojne komplikacije koje nastaju tokom života.

Prema smernicama *Joint National Commission*, u cilju skrininga za *PA* preporuka je da se testiraju svi pacijenti sa: 1. hipertenzijom stadijuma 2 (>160–179/100–109mmHg), stadijuma 3 (>180/110 mmHg), ili rezistentnom hipertenzijom na višestepenoj terapiji (>140/90mmHg); 2. spontanom hipokalijemijom ili hipokalijemijom izazvanom diureticima; 3. hipertenzijom i adrenalnim incidentalomom; 4. pozitivnom porodičnom anamnezom za ranu hipertenziju ili cerebrovaskularni događaj (9). U porodičnoj anamnezi kod kojih se moždani udar desio pre 40. godine života, potrebno je razmišljati o glukokortikoid posredovanom aldosteronizmu (*GPA*), što nije bio slučaj kod našeg pacijenta.

Najčešći razlozi za postojanje primarnog aldosteronizma su idiopatska bilateralna adrenalna hiperplazija (*IHA*) i adrenalni adenomi (*APA*), koji su uglavnom mali produkujući adenomi (manji od 2 cm). Postoji nekoliko razlika između ova dva klinička entiteta: 1. *APA* su hirurški izlečivi, dok *IHA* nije; 2. *APA* imaju veći stepen

produkcije aldosterona u odnosu na druge forme; 3. posledice i komplikacije su teže kod *APA* (10, 11). Budući da je naš pacijent imao morfološki supstrat, adenom na desnoj nadbubrežnoj žlezdi veličine 9 mm, uz podatak o rano nastaloj hipertenziji sa spontanom hipokalijemijom, testiranje je započeto u pravcu primarnog aldosteronizma. Vizuelizacija nadbubrežnih žlezda preporučena je kod svih pacijenata sa dokazanim aldosteronizmom, a snimanje magnetnom rezonancom nije informativnije u odnosu na kompjuterizovanu tomografiju (12).

Ukoliko postoji hipokalijemija, pre početaka testiranja potrebno je da se nadoknadi kalijum, a zatim se uzimaju uzorci krvi za aldosteron i PRA ili renin na aldosteron neutralnoj terapiji (*washout*), a potom se analizira ALDO/PRA odnos (*ARR*), s obzirom na to da kod jednog broja pacijenata može postojati *PA* sa urednim vrednostima ovih hormona (36–48%). U literaturi se spominje značajniji *ARR* koji bi ukazao na mogući aldosteronizam 20–40, dok većina autora smatra da *ARR* preko 35 ima 100% senzitivnost i oko 92% specifičnost. Ipak, drugi, pored pozitivnog *ARR,* u kriterijum za PA svrstavaju i povišene vrednosti aldosterona. Ukoliko su rezultati nekonkluzivni, kao u slučaju našeg pacijenta, potrebno je da se urade dodatni dijagnostički – funkcionalni testovi, tzv. potvrdni testovi (oralno opterećenje natrijumom, kaptoprilski test, akutna intravaskularna ekspanzija volumena – infuzioni test, fludrokortizonski test).

U slučaju našeg pacijenta urađena su dva supresiona testa, najpre kaptoprilski, a zatim infuzioni test. U kaptoprilskom testu pacijentu se daje 50 mg kaptoprila, a test se tumači tako što u osoba koje nemaju *PA* vrednost aldosterona pada za više od 20% u odnosu na inicijalnu vrednost. Odnosno, vrednost aldosterona treba da padne ispod 15 ng/dL u 120. minutu. U vodiču *Diagnosis and management of primary hyperaldosteronism in patients with hypertension: a practical approach endorsed by the British and Irish Hypertension Society* opisani su strožiji kriterijumu, da kod zdravih osoba vrednosti aldosterona treba da padnu za 30% u odnosu na aldosteron u nultom minutu, tj. na 8 ng/dL na kraju testa. Dok odnos ALDO/PRA posle 2h treba da bude ispod 30 (13). Senzitivnost testa je 90–100%, a specifičnost 50–80%. U odnosu na baznu vrednost aldosterona (30,87 ng/dL), u ovom testu kod našeg pacijenta došlo je do supresije sekrecije aldosterona (120 minut: 15,44 ng/dL), što, prema mišljenju nekih autora, isključuje postojanje *PA*, dok kod drugih ne. Istovremeno, došlo je do porasta vrednosti PRA, što bi dodatno više govorilo protiv postojanja *PA*, uz oprez pri zaključivanju zbog i dalje niske vrednosti PRA.

U infuzionom testu pacijent se opterećuje izotoničnim slanim rastvorom datim *i.v.* 500 mL/h tokom 4–6 sati, koji dovodi do supresije aldosterona u serumu na <10 ng/dL kod zdravih, ali ne i u primarnom aldosteronizmu. Međutim, stav pojedinih autora je da na kraju testa supresija aldosterona na 5–10 ng/dL je siva zona, dok su drugi definisali *cut-off* vrednost na 6,8 ng/dL (14, 15, 16, 17). Tako, kod našeg pacijenta aldosteron je suprimovan do 10,39 ng/dL, što bi predstavljalo graničnu supresiju.

Veliki značaj u procesu testiranja ima prekonoćni supresioni test deksametazonom 1 mg, koji bi mogao da sugeriše u pravcu glukokortikoid posredovanog aldosteronizma (*GPA*). *GPA* predstavlja autozomno dominantnu naslednu formu aldosteronizma, kod kojeg postoji „ektopično" lučenje aldosterona iz zone retikularis. Takvo stanje viška mineralokortikoda je pod uticajem ACTH, te se postavljanjem dijagnoze ovako retke forme bolesti lečenje zasniva na dugotrajnoj primeni malih doza kortikosteroida. Nakon prekonoćnog supresionog testa deksametazonom (1 mg) uzeti su uzorci za analizu *RAAS*, kojima je isključeno postojanje *GPA* kod našeg pacijenta.

Lečenje PA se zasniva na upotrebi farmakološke terapije ili operativnom lečenju. Prva linija izbora medikamenata su mineralokortikoidni antagonisti (spironolakton, eplerenon), glukokortikoidi i drugi diuretici koji štede kalijum (trimateren, amilorid). Uobičajene doze spironolaktona su 50–200 mg, a normalizacija krvnog pritiska se očekuje za 4 do 8 nedelja. Neželjeni efekti ovog leka su ginekomastija, smanjenje libida, impotencija kod muškarca, dok kod žena mogu da se jave iregularni menstrualni ciklusi. Zamena za spironolakton je eplerenon (50 mg dva puta na dan), ali je dosta skuplji i manje potentniji mineralokortikoidni antagonist. Kod pacijenata sa *IHA* uspešno lečenje se zasniva na primeni kalcijumskih blokatora, a naročito i ACE inhibitora, koji smanjuje stvaranje *Ang II.*

Adrenalektomija je terapija izbora za adenome (*APA*), međutim, opcije koje su u fokusu proučavanja su delimična adrenelektomija, tj. klinasta resekcija i ekstrakcija adenoma (*APA*) ili adrenelektomija sa očuvanjem medule. U slučajevima postojanja kontraindikacija za adrenalektomiju opisano je nekoliko prikaza slučaja primene perkutane injekcije etanola u *APA* (18, 19).

Zaključak:

Prikazali smo pacijenta sa dijagnostikovanom hipertenzijom u mlađoj životnoj dobi i registrovanom spontanom hipokalijemijom. S obzirom na to da je CT-om viđen maleni adenom (9 mm), inicijalno je razmišljano u pravcu aldosteronizma, tj. aldosteron produkujućeg adenoma. Nakon kompletnog testiranja zaključeno je: 1. da se kod pacijenta povremeno registruje suprimovana plazma reninska aktivnost uz vrednost aldosterona, u opsegu za zdrave osobe 2; odnos aldosteron/renin je povišen; 3. u kaptoprilskom i infuzionom testu aldosteron je suprimovan na granične vrednosti za testove 4; porodična anamneza nije bila opterećena hipertenzijom i vaskularnim događajima uz uredan prekonoćni deksametazonski test (*GPA*). U ovom trenutku, na osnovu kriterijuma koje podržava jedna grupa autora, mogli bismo isključiti primarni aldosteronizam, dok na osnovu strožijih kriterijuma, podržanih od strane nekih autora, ovakvi rezultati bi i dalje govorili u prilog postojanja autonomne produkcije aldosterona. Uprkos različitim preporukama, adrenalno vensko semplovanje bi imalo najveći dijagnostički značaj u dobijenim rezultatima ***sivih zona***.

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DIAGNOSTIC UNCERTAINTY IN PRIMARY ALDOSTERONISM

Abstract: Aldosterone is a mineralocorticoid hormone originating from the glomerulosa zone of the adrenal cortex. Its main mechanism of action involves the reabsorption of sodium along with the secretion of potassium and hydrogen ions. It is the final hormonal signal in the renin-angiotensin-aldosterone system, which participates in the regulation of circulating volume and systemic vascular resistance. Hypokalemia and hypertension are key indicators for diagnosing hyperaldosteronism. We present the case of a patient who was diagnosed with hypertension at the age of 30. Hypokalemia was first recorded in his 59th year (2023) with a level of 3.1 mmol/L. The analyzed RAAS markers showed an elevated ALDO/PRA ratio. Computed tomography revealed a change in the right adrenal gland, measuring 9 mm. Given that the baseline aldosterone values were within the normal range for the healthy population, with a suppressed renin activity peak in one sample, primary aldosteronism was suspected. Consequently, confirmatory suppression tests were required to establish the diagnosis.

Keywords: secondary hypertension, aldosteronism, hypokalemia

Introduction:

Aldosterone is a hormone produced by the adrenal cortex and is a key component of the complex renin-angiotensin-aldosterone system (RAAS) (1). Under physiological conditions, it regulates electrolyte balance by increasing sodium reabsorption, which also draws water along with it, and by secreting potassium ions (2). One potential cause of increased aldosterone production is adrenal gland pathology. In

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addition to the RAAS, other regulatory mechanisms, though less influential, include adrenocorticotropic hormone (ACTH), atrial natriuretic peptide (ANP), and dopamine. The majority of patients suffer from primary essential hypertension, with 5 to 10% having secondary endocrine hypertension, including aldosteronism, Cushing's syndrome, or thyroid disease (3). The most common causes of primary aldosteronism are aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia (IHA), while familial forms of the disease are less common (4).

A case report:

A 60-year-old male patient was diagnosed with high blood pressure in his 30s. Hypokalemia (K: 3.1 mmol/L) was first detected at the age of 59 and persists even after discontinuation of diuretic therapy. Nephrological evaluation ruled out renal artery stenosis. In an outpatient setting, the RAAS axis was analyzed, which revealed suppressed plasma renin activity (0.7 μIU/mL; reference values: 2.8–39.9). The aldosterone value was within the normal range for healthy individuals (19.3 ng/dL), and the ALDO/PRA ratio was borderline elevated (ARR = 27).

During hospitalization at the Clinic for Endocrinology, Diabetes, and Metabolic Diseases of the UKCS, tests were performed to investigate primary aldosteronism. Computed tomography revealed a small lesion in the right adrenal gland measuring 9 mm, and endocrinological functional tests ruled out autonomous cortisol secretion and catecholamine excess. On aldosterone-neutral therapy, aldosterone values were within the reference range for a healthy population, with suppressed PRA in one sample (ALDO 345.5–254.4, PRA <0.3–5). As a result, the diagnosis of primary aldosteronism could not be excluded. Consequently, confirmatory suppression tests were performed to establish the diagnosis (Tables 1 and 2).

Table 1. Captopril test

Captopril test		
	ALDO ng/dL	PRA ng/mL/h
0 min	30	<0,3
120 min	15,44	0,48

Table 2. Infusion test

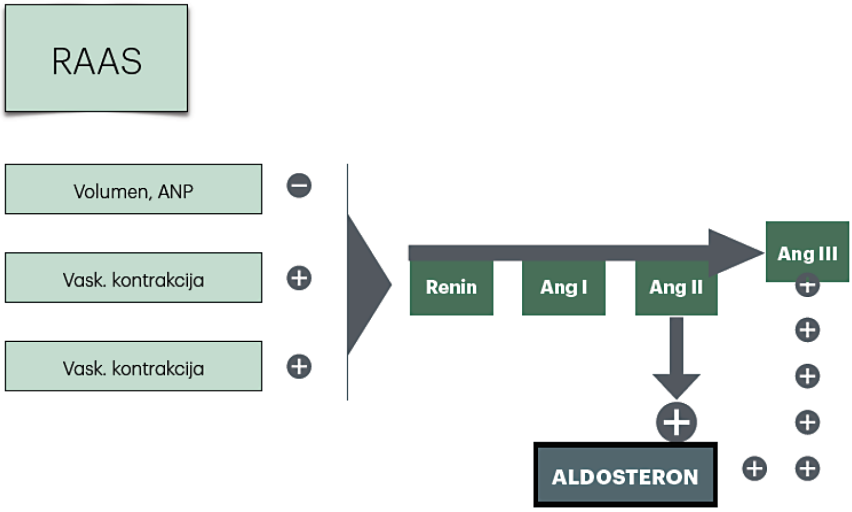
Infusion test		
	ALDO ng/dL	PRA ng/mL/h
0 min	21,83	0,35
30 min	13,59	1,70
60 min	18,46	<0,3
120 min	11,66	<0,3
240 min	10,39	1,1

Atrial fibrillation had previously been diagnosed and was treated with radio-frequency ablation. In 2023, the patient experienced a myocardial infarction, during which two stents were implanted. A heart ultrasound revealed hypokinesia to akinesia of the basal segment of the septum and the basal segment of the inferoposterior wall (EF 60%). The family history was not significant for early hypertension or cardio cerebrovascular events. The patient is a former smoker.

Discussion:

The mineralocorticoid hormone aldosterone plays a key role in maintaining circulating blood volume and serum potassium concentrations. These processes, through a feedback loop, regulate aldosterone secretion from the glomerulosa of the adrenal cortex (Scheme 1). Aldosterone inhibitors include atrial natriuretic peptide (ANP) and local dopamine, while renin synthesis is activated by reduced circulating volume and beta-adrenergic stimulation of sympathetic nerves (5). Elevated potassium levels inhibit renin synthesis, while directly stimulating aldosterone secretion, which highlights the role of the renin-angiotensin-aldosterone system (RAAS) as a protective compensatory mechanism against hyperkalemia. In contrast, hypokalemia reduces aldosterone synthesis, and diuretics that promote potassium loss influence both plasma renin and aldosterone concentrations. Renin is converted to angiotensinogen, which is then converted to angiotensin I; under the influence of angiotensin-converting enzyme (ACE), angiotensin I is further converted to angiotensin II, which in turn stimulates aldosterone release.

Scheme 1. *RAAS*



The final product of angiotensin II is metabolized in the liver to form angiotensin III, a heptapeptide that also stimulates aldosterone secretion (6). Prostaglandins I2 and E2 play a significant role, and it has been shown that metoclopramide increases aldosterone secretion. Two key factors that lead doctors to suspect aldosteronism are: 1. hypertension, particularly when it occurs at a younger age, and 2. hypokalemia. The predictive value of the presence of both components is 50% (7). In younger patients, primary aldosteronism may be asymptomatic. When symptoms do occur, patients commonly complain of headache, facial flushing, and tinnitus. However, long-term uncontrolled hypertension can lead to vision impairment, altered consciousness, and hypertensive encephalopathy. Hypokalemia can cause fatigue, weakness, constipation, and heart rhythm disturbances, but approximately 60% of people with primary aldosteronism are normokalemic (8). Consequently, it is crucial to recognize this clinical condition due to the many complications that can arise over time.

According to the "Joint National Committee" guidelines, screening for primary aldosteronism (PA) is recommended for all patients with: 1. stage 2 hypertension (>160/100–109 mmHg), stage 3 hypertension (>180/110 mmHg), or resistant hypertension despite multi-drug therapy (>140/90 mmHg); 2. spontaneous hypokalemia or hyperkalemia induced by diuretics; 3. hypertension and adrenal incidentaloma; 4. a positive family history of early hypertension or cerebrovascular events (9). In cases of a family history of stroke before 40 years of age, glucocorticoid-mediated aldosteronism (GPA) should be considered, although this was not the case for our patient.

The most common causes of primary aldosteronism are idiopathic bilateral adrenal hyperplasia (IHA) and adrenal adenomas (APA), with the latter typically being small, aldosterone-producing adenomas (less than 2 cm). There are several key differences between these two clinical entities: 1. APA is surgically curable, while IHA is not; 2. APAs produce higher levels of aldosterone compared to IHA; 3. The consequences and complications are more severe with APA (10, 11). Since our patient had a morphological substrate–specifically, a 9 mm adenoma in the right adrenal gland–along with a history of early-onset hypertension and spontaneous hypokalemia, testing for primary aldosteronism was initiated. Visualization of the adrenal glands is recommended in all patients with confirmed aldosteronism, and magnetic resonance imaging (MRI) is no more informative than computed tomography (CT) in this context (12).

If hypokalemia is present, potassium should be replenished before initiating testing. Afterward, blood samples for aldosterone and plasma renin activity (PRA) or renin should be taken while the patient is on aldosterone-neutral therapy (washout). The ALDO/PRA ratio (ARR) should then be analyzed, as some patients with primary aldosteronism (PA) may have normal values of these hormones (36–48%). The literature suggests a more significant ARR of 20–40 as indicative of possible aldosteronism, while most authors agree that an ARR over 35 has 100% sensitivity and approximately 92% specificity. However, some clinicians also include elevated aldosterone levels, in addition to a positive ARR, as a criterion for diagnosing PA. If the results are inconclusive, as in the case of our patient, additional diagnostic or functional tests–known as confirmatory tests–should be performed. These include oral sodium load, the captopril test, acute intravascular volume expansion (infusion test), and the fludrocortisone test.

In the case of our patient, two suppression tests were performed: first the captopril test, followed by the infusion test. In the captopril test, the patient was given 50 mg of captopril. The test is interpreted based on the fact that, in individuals without primary aldosteronism (PA), aldosterone levels should decrease by more than 20% from the baseline. Specifically, aldosterone values should fall below 15 ng/dL. The guideline “Diagnosis and Management of Primary Hyperaldosteronism in Patients with Hypertension: A Practical Approach Endorsed by the British and Irish Hypertension Society” outlines a stricter criterion, stating that in healthy individuals, aldosterone levels should drop by at least 30% from baseline (i.e., to below 8 ng/dL). Additionally, the ALDO/PRA ratio after 2 hours should be below 30 (13). The sensitivity of the captopril test is reported to be 90–100%, with specificity ranging from 50–80%. In our patient, the baseline aldosterone value was 30.87 ng/dL, and after the captopril test, aldosterone secretion was suppressed to 15.44 ng/dL. Some authors interpret this suppression as excluding the diagnosis of PA, while others do not. Simultaneously, there was an increase in PRA, which would typically argue

against PA. However, caution is needed when interpreting these results, given the still low PRA value.

In the infusion test, the patient is infused with an isotonic saline solution intravenously at 500 mL/h for 4–6 hours. This typically suppresses serum aldosterone to levels <10 ng/dL in healthy individuals, but not in those with primary aldosteronism (PA). However, some authors consider aldosterone suppression in the range of 5–10 ng/dL to be a gray area, while others set the cut-off at 6.8 ng/dL (14, 15, 16, 17). In our patient, aldosterone was suppressed to 10.39 ng/dL, which is considered borderline suppression. A key test in the diagnostic process is the overnight suppression test with 1 mg of dexamethasone, which could suggest glucocorticoid-mediated aldosteronism (GPA). GPA is an autosomal dominant, hereditary form of aldosteronism characterized by "ectopic" aldosterone secretion from the zona reticularis. In this condition, excess mineralocorticoids are regulated by ACTH. Diagnosis of this rare form of the disease leads to treatment with long-term, low-dose corticosteroids.

Treatment of primary aldosteronism (PA) involves either pharmacological therapy or surgical intervention. The first-line pharmacological treatment includes mineralocorticoid antagonists (spironolactone, eplerenone), glucocorticoids, and other potassium-sparing diuretics (such as triamterene and amiloride). Typical doses of spironolactone range from 50–200 mg daily, with blood pressure normalization expected within 4 to 8 weeks. Side effects of spironolactone include gynecomastia, decreased libido, and impotence in men, while women may experience irregular menstrual cycles. Eplerenone (50 mg twice daily) can be used as a substitute for spironolactone; however, it is more expensive and less potent as a mineralocorticoid antagonist. In patients with idiopathic bilateral adrenal hyperplasia (IHA), treatment is typically based on calcium channel blockers and, particularly, angiotensin-converting enzyme (ACE) inhibitors, which reduce the production of angiotensin II. For adrenal adenomas (APA), adrenalectomy is the preferred treatment. However, alternative surgical options being explored include partial adrenalectomy (wedge resection) and adrenalectomy with preservation of the adrenal medulla. In cases where adrenalectomy is contraindicated, several case reports have described the use of percutaneous ethanol injection for APA (18, 19).

Conclusion:

We presented a patient with a diagnosis of hypertension at a younger age and spontaneous hypokalemia. Given the presence of a small 9 mm adenoma on CT, primary aldosteronism, specifically aldosterone-producing adenoma (APA), was initially suspected. After a comprehensive work-up, the following conclusions were made: 1. The patient exhibited occasional suppression of plasma renin activity, with aldosterone levels within the reference range for healthy individuals. 2. The aldoste-

rone/renin ratio (ARR) was elevated. 3. Both the captopril and infusion tests showed aldosterone suppression to the threshold values for these tests. 4. Family history was not significant for hypertension or vascular events, and the overnight dexamethasone test was negative for glucocorticoid-mediated aldosteronism (GPA). Based on the criteria supported by one group of authors, we could exclude primary aldosteronism. However, according to stricter criteria advocated by other authors, these results might still suggest the possibility of autonomous aldosterone production. Despite varying recommendations, adrenal venous sampling would provide the most definitive diagnostic information in cases with ***gray zone*** results.

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