TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245 *Case Report*

The Silent Long-Term Damage of Resistant Hypertension: A Clinical Case Report

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Abstract

Background/Aim: Resistant hypertension (RH) is a complex clinical condition associated with substantial cardiovascular and renal morbidity. Persistent blood pressure (BP) elevation despite optimal multidrug therapy should prompt a careful search for secondary causes and hypertension-mediated target organ damage. Chronic kidney disease (CKD) and sustained activation of the renin–angiotensin–aldosterone system (RAAS) are frequently involved, often resulting in a prolonged subclinical course. This case report aims to highlight the clinical importance of a structured diagnostic approach to resistant hypertension in the context of a hypertensive emergency.

Case: A 56-year-old man without previous medical follow-up presented with severe hypertension accompanied by headache and epigastric discomfort. BP measurements revealed marked inter-arm differences and values consistent with a hypertensive emergency. Laboratory evaluation showed impaired renal function, hypokalemia, and significant proteinuria. Imaging and echocardiographic assessment demonstrated chronic kidney disease, left ventricular hypertrophy, pulmonary congestion, and ascending aortic dilatation. Further hormonal evaluation revealed elevated renin and aldosterone levels with a low aldosterone to renin ratio, supporting secondary hyperaldosteronism related to CKD and exacerbated by frequent nonsteroidal anti-inflammatory drug use. BP was controlled with intravenous antihypertensive therapy followed by intensive oral multidrug treatment, including diuretics, renin–angiotensin system blockade, and an aldosterone antagonist.

Conclusion: This case demonstrates that long-standing, undiagnosed hypertension may present as a hypertensive emergency accompanied by advanced target organ damage. Hypervolemia and the RAAS play a critical role in the development of RH, particularly when combined with CKD and nonsteroidal anti-inflammatory drug use. Low aldosterone to renin ratio levels, accompanied by elevated renin and aldosterone levels, serve as a valuable marker for ruling out primary adrenal pathology and indicate secondary hyperaldosteronism. Although the difference in BP between the arms initially suggests structural vascular abnormalities, the underlying etiology is RAAS activation triggered by CKD and hypervolemia. This case highlights the importance of regular BP measurements and a systematic approach, including assessment of the RAAS profile, fluid status, and medication history, for accurate diagnosis in RH.

Keywords: Resistant hypertension, Secondary hypertension, Hypertensive emergency, Chronic kidney disease, Secondary hyperaldosteronism, Target organ damage, Renin-angiotensin-aldosterone system, Aldosterone to renin ratio

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Received: *February 7, 2026*
Accepted: *March 31, 2026*
Published: *April 17, 2026*

Turk J Int Med 2026;8:10 DOI: 10.46310/tjim.1884135

Cite as: Erarslan S, Yılmaz Göde C, Paşalı Kilit T. The silent long-term damage of resistant hypertension: a clinical case report. Turk J Int Med 2026;8:10. doi:10.46310/tjim.1884135.

INTRODUCTION

Hypertension (HT) is a major and modifiable risk factor for cardiovascular disease [1]. Essential HT accounts for approximately 90–95% of all cases, while secondary HT is identified in about 5–10% of patients [2]. Secondary HT is defined as elevated blood pressure (BP) resulting from an identifiable underlying cause [3]. Certain clinical features should raise suspicion for secondary HT, including onset at a young age (under 30 years) or at an advanced age, HT accompanied by hypokalemia, presence of an adrenal adenoma, sudden deterioration in previously controlled BP, detection of a renal artery bruit on physical examination, resistant hypertension (RH), and a significant BP difference between extremities (a systolic difference ≥15 mmHg between the right and left arms). In such patients, secondary causes must be systematically investigated [4]. Among adults, the most common causes of secondary HT, in order of prevalence, include obstructive sleep apnea, primary hyperaldosteronism, and renovascular HT [5].

RH is defined as BP remaining ≥140/90 mmHg despite lifestyle modification and treatment with three different antihypertensive agents, one of which is a diuretic. If BP control is achieved with four or more medications, the condition is referred to as controlled resistant HT [6].

RH is common, especially in patients with chronic kidney disease (CKD), and its prevalence increases as kidney function declines. In the Chronic Renal Insufficiency Cohort (CRIC) study, apparent treatment-resistant HT was reported in 42% of individuals with established CKD. RH has been shown to significantly increase the risk of progression to end-stage renal disease and overall mortality. Subclinical volume overload and increased sodium sensitivity in the CKD population play a central role in the pathogenesis of RH. Impaired sodium excretion leads to persistent volume expansion, maintaining elevated BP and contributing to existing renal damage, thereby creating a pathophysiological vicious cycle [4].

This case aims to underscore the importance of a systematic clinical approach in patients with RH, with particular emphasis on investigating secondary etiologies and assessing HT-related target organ damage.

METHOD

RH is defined as BP remaining ≥140/90 mmHg despite adherence to lifestyle modifications and treatment with three antihypertensive agents of different classes, one of which should be a diuretic. When BP control is achieved only with the use of four or more antihypertensive medications, the condition is referred to as controlled RH [6]. This definition was applied prospectively during the diagnostic and therapeutic evaluation of the patient.

A stepwise diagnostic algorithm was applied in accordance with established clinical guidelines for the evaluation of secondary hypertension [1]. Secondary hypertension was suspected in cases of RH, hypertensive emergency, hypokalemia, and a significant right–left arm BP difference.

In the initial phase, BP measurements were verified using appropriate techniques; medication compliance, lifestyle factors, and exogenous factors such as nonsteroidal anti-inflammatory drug (NSAID) use were investigated. A detailed medical history and focused physical examination were performed to identify clinical clues that could indicate specific secondary etiologies.

Basic laboratory tests included serum electrolytes, renal function tests, fasting glucose, lipid profile, thyroid-stimulating hormone level, and urinalysis. In the presence of hypokalemia and RH, plasma renin activity and plasma aldosterone levels were measured for screening purposes for primary and secondary hyperaldosteronism, and the aldosterone/renin ratio (ARR) was then calculated.

Renal parenchymal disease and renovascular hypertension were evaluated using renal ultrasonography and renal artery doppler imaging. Additional vascular investigations and a detailed physical examination were performed to rule out subclavian artery stenosis, aortic pathologies, and large vessel vasculitis due

to the right–left arm BP difference. Due to limited contrast imaging because of renal dysfunction, non-contrast imaging methods were preferred.

In line with clinical suspicion, endocrine causes were systematically ruled out, and an evaluation was performed for pheochromocytoma and Cushing syndrome. Additionally, the possibilities of obstructive sleep apnea and drug-induced hypertension were also considered in the diagnostic process.

This diagnostic approach, based on systematic and clinical findings, has enabled the targeted evaluation of secondary hypertension etiologies, the accurate etiological classification, and the development of a mechanism-based treatment plan.

Consent was obtained from the patient for the publication of this case report and accompanying images.

CASE PRESENTATION

A 56-year-old man presented to a primary care clinic with complaints of epigastric burning and headache localized to the occipital and nuchal regions. His arterial BP was measured as 220/160 mmHg, prompting referral to our outpatient clinic. On evaluation, BP was 240/150 mmHg in the left arm and 180/130 mmHg in the right arm. He had no known comorbidities or cardiovascular risk factors and reported no hospital admissions for a long period. However, he disclosed frequent use of NSAIDs. Physical examination was unremarkable except for severe hypertension and a BP difference between the right and left arms.

Initial laboratory tests revealed elevated serum creatinine, hypokalemia, and +3 proteinuria on urinalysis. With a preliminary diagnosis of secondary HT, the patient was admitted for further evaluation and management.

A systolic BP difference of ≥10 mmHg between the right and left arms is considered clinically significant, whereas differences of ≥15–20 mmHg warrant further evaluation for underlying vascular pathologies. In such cases, subclavian artery disease, aortic dissection, coarctation of the aorta, large-vessel vasculitis, and peripheral arterial disease should be considered in the differential diagnosis. On physical examination, peripheral pulses in both the upper and lower extremities were symmetrically palpable, with no evidence of pulse asymmetry or diminution. No temperature gradient was observed between the upper and lower extremities.

Contrast-enhanced imaging was not performed due to elevated serum creatinine levels. Therefore, color Doppler ultrasonography was requested for the abdominal aorta, and no additional pathological findings were detected. CT was taken of the thorax and upper abdomen; Increased cardiothoracic index, 15 mm pleural effusion in the right hemithorax, and pulmonary edema in both lungs were observed. In addition, dilatation reaching 46 mm in the ascending aorta and 37 mm in the main pulmonary artery was detected. Splenomegaly was detected. There was no adrenal gland pathology. A slight reduction in kidney size was detected. Bilateral lower extremity arterial and venous Doppler ultrasonography findings were within normal limits.

A concurrent cardiology consultation was obtained. Transthoracic echocardiography (ECHO) demonstrated left ventricular hypertrophy (LVH), a preserved ejection fraction (EF) of 60%, an ascending aortic diameter of 43 mm, mild mitral regurgitation, and minimal tricuspid regurgitation. No additional pathological findings were identified on further evaluation.

The patient was evaluated for a hypertensive emergency. There was no alteration in mental status and no chest pain. Electrocardiography demonstrated a normal sinus rhythm. Fundoscopic examination revealed optic disc edema, and in the presence of elevated serum creatinine and significant proteinuria, the clinical picture was consistent with a hypertensive emergency. Intravenous glyceryl trinitrate was initiated, with a target of reducing BP to 150–160/100–110 mmHg within the first four hours, followed by gradual achievement of normotension over the subsequent 48 hours.

Additional laboratory investigations, including thyroid function tests, lipid profile, fasting plasma glucose, HbA1c, and serum electrolytes (Na, K, Ca, P), were within normal limits. Renal ultrasonography and renal artery doppler ultrasonography showed bilaterally reduced renal parenchymal thickness and increased echogenicity consistent with grade 1 CKD. No renal artery stenosis or adrenal pathology was detected.

Nephrology evaluation included a 24-hour urine collection, which showed proteinuria of 2061 mg/day and albuminuria of 1362 mg/day. Immunological tests for vasculitis were performed; complement levels were normal, and antinuclear antibody and antineutrophil cytoplasmic antibody tests were negative. Due to hypokalemia, plasma renin activity and aldosterone levels were measured. Renin activity was elevated at 11.52 ng/mL/h, and aldosterone was 44.3 ng/mL, yielding an aldosterone to renin ratio of 3.84, suggestive of secondary hyperaldosteronism. After a vanillylmandelic acid diet, 24-hour urinary catecholamines, metabolites, and cortisol levels were assessed and found to be normal.

Given the presence of splenomegaly and anemia, a hematology consultation was requested. Portal vein Doppler ultrasonography was normal. Peripheral blood smear showed normal erythroid and platelet lineages without atypical cells. Serum immunoglobulin levels were within normal limits. Protein electrophoresis and immunofixation revealed no pathological findings. Free light chain analysis showed elevated lambda (105 mg/L) and kappa (84.8 mg/L) levels, but the kappa/lambda ratio was preserved, excluding monoclonal gammopathy.

In the context of hypertensive emergency, hypervolemia, CKD, LVH, and fundoscopic edema, renal HT and hypertensive nephropathy were considered the most likely diagnoses. Intravenous nitroglycerin and diuretic therapy were initiated, with close monitoring of urine output and vital signs. After 48 hours, arterial BP decreased to approximately 140/90 mmHg, intravenous antihypertensive agents were discontinued, and oral triple antihypertensive therapy (an ACE inhibitor, a diuretic, and a calcium channel blocker) was initiated. Follow-up chest radiography demonstrated regression of pleural effusion, allowing discontinuation of intravenous diuretics.

DISCUSSION

HT is defined as an elevation of intravascular pressure within the arterial system. If not detected early and treated effectively, it may lead to target organ damage by affecting the heart, kidneys, central nervous system, and eyes. Such injury is not solely related to the absolute increase in BP but also to the cumulative effects of long-standing HT. Accordingly, optimal management and regular follow-up of HT patients play a pivotal role in preventing end-organ damage [3].

In our patient, preserved EF in the presence of LVH, ascending aortic dilatation, pleural effusion, and pulmonary edema is consistent with cardiovascular complications of HT and suggests a clinical picture of heart failure with preserved EF. Previous studies have shown that chronic HT is a major contributor to diastolic dysfunction, secondary LVH, heart failure, and, over time, aortic dilatation [3].

HT is also an independent risk factor for the development of CKD. In patients with CKD, RH frequently coexists with reduced glomerular filtration rate, increased albuminuria, and progressive target organ damage [4]. In our patient, the frequent use of NSAIDs may have further aggravated the process of renal injury. A study published in 2020 emphasized that NSAID use, through inhibition of prostaglandin synthesis, reduces renal perfusion and increases the risk of acute kidney injury as well as the development of CKD in the long term [5]. Prolonged HT and heart failure may lead to a reduction in effective circulating volume and renal hypoperfusion, thereby increasing renin secretion from juxtaglomerular apparatus cells and resulting in chronic activation of the RAAS [6]. In our patient, concomitant NSAID use likely worsened renal hypoperfusion, facilitating the development of secondary hyperaldosteronism.

At presentation and during hospitalization, the patient exhibited resistant HT, elevated creatinine, stage 3b CKD, proteinuria, and secondary hyperaldosteronism. Given the absence of prior medical

follow-up, anemia secondary to CKD was also likely present. This clinical profile highlights the combined impact of uncontrolled HT and medication use on CKD progression and its associated complications.

In patients with secondary HT, careful evaluation for endocrine etiologies is of particular importance. The literature indicates that approximately 10–15% of secondary HT cases are of endocrine origin, with pheochromocytoma, primary hyperaldosteronism, and Cushing syndrome being conditions that should be prioritized for exclusion [7,8]

Hypertensive emergency is defined by severe BP elevation accompanied by evidence of acute target organ damage and requires prompt yet controlled BP reduction [9]. In our patient, the presence of fundoscopic edema, pulmonary edema, renal dysfunction, and resistant HT fulfilled the criteria for hypertensive emergency. Although treatment goals may vary depending on the extent and severity of target organ involvement, current recommendations generally advise reducing mean arterial pressure by approximately 20–25% within the first hours, as more aggressive reductions may precipitate ischemic complications [10].

In this context, the use of intravenous nitroglycerin was an appropriate therapeutic choice, given the concomitant pulmonary congestion and acute target organ involvement. Beyond rapid BP control, identifying underlying precipitating factors and investigating secondary causes of HT are essential to prevent recurrence in patients with hypertensive emergencies.

The RAAS is a neurohormonal mechanism that plays a fundamental role in regulating BP and sodium balance. Excess aldosterone increases sodium retention and potassium excretion in the distal nephron, leading to volume enlargement and hypertension. Chronic mineralocorticoid receptor activation is not limited to hemodynamic effects, but accelerates target organ damage by triggering inflammation, fibrosis, and structural restructuring in cardiovascular and renal tissue [6].

Plasma renin activity (PRA) and ARR calculated from plasma aldosterone level are the main screening tests in the differential diagnosis of hyperaldosteronism. In primary hyperaldosteronism, aldosterone is high, renin is suppressed, and ARR is significantly increased; in secondary hyperaldosteronism, both parameters are high, but ARR is usually in the normal or low-normal range. Although an ARR above 20–30 is considered in favor of primary hyperaldosteronism, it should be noted that threshold values may vary depending on the measurement method. In order to interpret the test correctly, hypokalemia should be corrected, drugs that may affect it should be discontinued if possible, sampling should be performed in the appropriate position and timing, and excessive sodium restriction should be avoided [6].

PRA and aldosterone levels were evaluated in the present case; renin (11.52 ng/mL/hour) and aldosterone (44.3 ng/mL) were found to be high, while ARR of 3.84 was found to be compatible with secondary hyperaldosteronism. Considering our patient's CKD, hypertensive nephropathy, and volume burden, RAAS activation was thought to be secondary and adaptive. These findings support the persistence of the association between RH and kidney damage through the RAAS.

In our case, CKD-associated RAAS activation and secondary hyperaldosteronism contributed to disease severity by reinforcing a cycle of hypervolemia and RH. Consequently, volume control with diuretics, RAAS blockade, and the addition of an aldosterone antagonist played a key role in achieving a favorable clinical response.

CONCLUSION

HT may remain clinically silent for prolonged periods, and delayed recognition can allow progressive target organ damage to develop before clinical presentation. In the present case, long-standing, previously undiagnosed hypertension manifested as a hypertensive emergency, with evidence of hypertensive nephropathy, cardiac involvement, and retinal changes. Frequent use of NSAIDs may

have contributed to kidney dysfunction and increased BP, further complicating the clinical course.

This case underscores the complex interplay between chronic kidney disease, volume overload, and RAAS activation in the pathogenesis of RH. Markedly elevated renin and aldosterone levels in the presence of a low ARR supported secondary hyperaldosteronism rather than primary adrenal pathology, highlighting the importance of contextual interpretation of biochemical findings. The significant inter-arm BP difference appropriately prompted evaluation for secondary vascular causes; however, major structural vascular pathologies were excluded. Instead, CKD-associated RAAS activation and hypervolemia emerged as the principal mechanisms sustaining RH and contributing to target organ damage.

Overall, this case illustrates that in patients presenting with hypertensive emergency and RH, a systematic diagnostic approach including assessment of RAAS parameters, volume status, medication history, and secondary etiologies is essential for accurate pathophysiological characterization and mechanism-based therapy. Early identification and targeted modulation of RAAS activity and volume overload may mitigate further renal and cardiovascular deterioration and improve clinical outcomes.

Abbreviations: HT: Hypertension, **BP:** blood pressure, **RH:** resistant hypertension, **NSAID:** Nonsteroidal Anti Inflammatory Drugs, **CKD:** Chronic kidney disease, **LVH:** Left Ventricular Hypertrophy, **EF:** Ejection Fraction, **RAAS:** Renin-Angiotensin-Aldosterone System, **ARR:** Aldosterone to Renin Ratio, **PRA:** Plasma renin activity, **ECHO:** Transthoracic echocardiography

Article Information Form

Acknowledgments: *We are indebted to the patient who participated in this study.*

Financial Disclosure: *There is no institution or person supporting this study.*

Conflicts of Interest: *None of the authors has a conflict of interest.*

Author Contributions: *Conceptualization: SE,CYG; Methodology: SE; Validation: SE,TPK; Investigation: SE,CYG; Resources: SE,CYG,TPK; Data curation: CYG; Writing – original draft: SE,CYG; Writing – review & editing: SE,CYG; Supervision: SE,TPK; Project administration: CYG*

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