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Malignant hypertension and pseudohyperaldosteronism associated with rifampicin therapy

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Abstract

We report the case of a 64-year-old woman who developed malignant and treatment-resistant arterial hypertension (HT) following the introduction of rifampicin for spondylodiscitis. Her previously stable blood pressure (BP) deteriorated rapidly despite extensive antihypertensive therapy. The utilisation of pharmaceutical agents that demonstrated minimal or no interaction with rifampicin has yielded only partial control over HT. Furthermore, biological settings provided evidence of pseudohyperaldosteronism. A comprehensive workup ruled out other secondary causes of HT. BP normalized progressively after rifampicin withdrawal, without additional therapeutic intervention. This temporal combination supports a causative role of rifampicin, potentially through mechanisms beyond drug interactions. We discuss hypotheses including corticosterone-driven pseudohyperaldosteronism resulting from cytochrome P450 induction, and pregnane X receptor agonism as contributors to HT. This case highlights the importance of recognizing rifampicin as a potential inducer of severe HT, even in patients receiving adjusted antihypertensive regimens, and suggests a pathophysiological mechanism that may extend beyond pharmacokinetic interferences.

Keywords Malignant hypertension, Rifampicin, Pharmacokinetic interference, Pseudohyperaldosteronism, Pregnane x receptor

Background

The destabilisation of previously controlled arterial hypertension (HT) following the introduction of rifampicin has been the subject of numerous descriptions [1–7]. A prospective study of 160 patients with a history of HT newly treated with rifampicin following a tuberculosis diagnosis revealed a significant increase in mean blood pressure (BP) values after six months of rifampicin treatment (+ 24/16 mmHg), despite the associated escalation of treatment (almost 20 times less monotherapy after 6 months of rifampicin compared to before) [2]. This destabilisation was reversible within 4 weeks of stopping rifampicin [2]. Prolonged use of rifampicin in these hypertensive patients is common, given the global incidence of tuberculosis (10.8 million/year) and

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the prevalence of HT (1 in 3 adults, or 1.3 billion people worldwide) [8, 9]. Almost one in two patients with tuberculosis was previously hypertensive, and may therefore be subject to destabilisation of BP control after the initiation of rifampicin [10]. Here we report the case of a 64-year-old woman treated with rifampicin for spondylodiscitis who presented with an episode of severe and resistant HT, complicated by malignant HT, uncontrolled despite switching to antihypertensive treatment that is not known to interact with rifampicin.

Case presentation

The patient was a 64-year-old woman at the time of hospitalization. She had a known history of HT since a decade, which was reasonably controlled with bisoprolol 5 mg o.d. and dual antihypertensive therapy at half of the recommended maximum dose: a combination of angiotensin II receptor blocker (ARB) and hydrochlorothiazide (Table 1). The patient had no relevant other disease or treatment. Her body mass index (BMI) was 26,3 kg/m^2, and she had neither acromegalic nor cushingoid morphotypes. The reason for hospitalization was the onset of visual disturbances, for which investigations concluded with a diagnosis of seronegative neuromyelitis optica. In this context, 5 days after admission, the patient received concomitantly courses of corticosteroids for 7 days and plasmapheresis 3 times a week for 3 weeks. At this stage of hospitalization, blood pressure (BP) was well controlled and serum potassium remained within the normal range despite thiazide use.

Two days after the end of corticotherapy, the patient developed mild hypokalemia associated with vomiting and diarrhea which lasted for a week, leading to the discontinuation of the thiazide. BP levels then began to rise slightly, about one month after the corticosteroid discontinuation. Unfortunately, the patient developed a spondylodiscitis and was started on cefazolin and rifampicin. Shortly thereafter, BP became markedly destabilized, with the onset of sustained grade III HT despite the administration of five antihypertensive agents at maximal doses (nebivolol, losartan, spironolactone, amlodipine, and moxonidine), along with worsening hypokalemia despite the lack of persisting digestive loss, high-dose oral potassium supplementation and progressively increased doses of spironolactone.

A comprehensive assessment was therefore undertaken to investigate secondary causes of HT and screen for potential complications. The first identified factor was the impact of rifampicin as a potent enzyme inducer, affecting the metabolism of most medications, including antihypertensives. Consequently, the patient's treatment was adjusted in collaboration with the pharmacy team.

Calcium channel blocker (CCB) therapy was discontinued, losartan was replaced with perindopril, and nebivolol was switched to bisoprolol. Terazosin was added to the regimen, while moxonidine and spironolactone were maintained. The prescription of hydrochlorothiazide was avoided due to persistent hypokalemia. Despite these therapeutic adjustments, no significant improvement in BP control was observed, and the patient developed grade III hypertensive retinopathy (Table 1).

The remainder of the secondary HT workup included normal urinary (nor)metanephrine levels, normal adrenal glands on abdominal CT-scan, a reassuring 24-hour urinary cortisol, elevated serum free cortisol at 56.7 nmol/l with an ACTH level of 23.9 ng/L, normal calcemia and parathormone levels, a renal artery Doppler ultrasound not showing stenosis, normal kidney and cardiac assessment and normal thyroid function. Both plasma renin activity and aldosterone levels were found to be suppressed, although interpretation was limited by the ongoing antihypertensive treatment and hypokalemia. Kaliuresis was increased at 80 mEq/g of creatinine on a spot urine. Besides, serum corticosteroid-binding globulin (CBG) level was slightly reduced at 46 mg/L, and serum levels of 21-desoxycortisol and 11-desoxycorticosterone were normal (0.09 µg/L and 0.11 µg/L, respectively) (Table 2). There was no liquorice consumption.

A few days later, rifampicin was discontinued after 6 weeks of treatment. BP and serum potassium levels gradually returned to normal, allowing progressive de-escalation of antihypertensive therapy to bisoprolol associated with triple combination of ARB, CCB, and hydrochlorothiazide, which was subsequently reduced to half the

Table 1 Evolution of the anti-hypertensive treatment and mean BP values during the patient hospitalization

	Before rifampicin therapy	In the beginning of rifampicin therapy	Treatment adaptations performed during rifampicin therapy	After the discontinuation of rifampicin therapy
Anti-hypertensive treatment	Losartan 50 mg o.d. Hydrochlorothiazide 12.5 mg o.d. Bisoprolol 5 mg o.d.	Losartan 100 mg o.d. Amlodipine 10 mg o.d. Nebivolol 5 mg o.d. Moxonidine 0.4 mg b.i.d. Spironolactone 100 mg o.d.	Perindopril 8 mg o.d. Bisoprolol 5 mg b.i.d. Terazosin 5 mg b.i.d. Moxonidine 0.4 mg b.i.d. Spironolactone 100 mg o.d.	Olmesartan 20 mg o.d. Amlodipine 5 mg o.d. Hydrochlorothiazide 12.5 mg o.d. Bisoprolol 5 mg o.d.
Average of systolic BP values	135 mmHg	200 mmHg	190 mmHg	120 mmHg

BP: blood pressure

Table 2 Comparison of main laboratory results obtained during and after discontinuation of rifampicin therapy

	Reference ranges	During rifampicin therapy	After discontinuation of rifampicin therapy
Plasma renin activity (ng/ml/h)	0.10–1.00	0.10	5.74
Serum aldosterone (ng/L)	< 264	< 14	132
Serum free cortisol (nmol/L)	7.3–57.8	56.7	12.4
Plasma ACTH (ng/L)	3.8–60.5	23.9	6.3
Serum CBG (mg/L)	20–102	46	30
Serum potassium (mmol/L)	3.5–5.1	2.8	3.9
Kaliuresis (mEq/g of creatinine)	< 13 if hypokalemia	80	47

ACTH: adrenocorticotropic hormone; CBG: corticosteroid-binding globulin

dose (Table 1). Endocrine reassessment showed a slightly elevated plasma renin activity level and a normal aldosterone concentration, as would be expected given the patient's ongoing treatment. Serum free cortisol levels had also normalized at 12.4 nmol/l with ACTH levels at 6.3 ng/L. Notably, serum potassium remained within the normal range despite the discontinuation of potassium supplementation, withdrawal of spironolactone, and the reintroduction of a thiazide diuretic (Table 2).

Discussion and conclusions

Rifampicin is a potent inducer of cytochrome P450 (CYP), in particular CYP3A4, as well as P-glycoprotein (P-gp), causing a drop in the effect of many drugs when used simultaneously [10]. For instance, rifampicin has been observed to reduce or even abolish the effect of CCB, indapamide, losartan, various beta-blockers (notably carvedilol, labetalol, metoprolol and propranolol) and prazosin [1, 3, 4, 10]. In the study by Liu et al. [10], the authors recommend treating HT in patients taking rifampicin with drugs whose activity will be little or not at all affected: angiotensin converting enzyme inhibitors, olmesartan or telmisartan, hydrochlorothiazide, certain beta-blockers (notably atenolol and bisoprolol), and spironolactone [10]. As the metabolism of moxonidine is independent of CYP and P-gp, and that of clonidine and nebivolol depends on CYP2D6, which is not induced by rifampicin, the activity of these 3 molecules should not be reduced in combination with rifampicin [10].

As reported by several authors [2, 5] and evidenced in the present clinical case, the use of interaction-free compounds with rifampicin does not always resolve the hypertensive picture, necessitating a therapeutic escalation sometimes with a polytherapy of 5 to 6 molecules [2, 5]. This phenomenon raises the question of other direct or indirect hypertensive effects of rifampicin. In the present case, the patient developed pseudohyperaldosteronism (characterised by resistant HT, hypokalemia with increased kaliuresis, reduced renin and aldosterone) after initiation of rifampicin, persisting during its use, then gradually resolving within few weeks of its discontinuation. In the absence of any consumption or administration of a known 11β-hydroxysteroid dehydrogenase inhibitor (i.e. liquorice, grapefruit, contraceptive medications, carbenoloxone or posaconazole), no explanation can be found for classic exogenous pseudohyperaldosteronism [11–13]. However, this pseudohyperaldosteronism is temporally consistent with rifampicin-mediated enzyme induction kinetics, peaking after one week of treatment and disappearing after two weeks of treatment discontinuation [14].

CYP3A4, strongly induced by rifampicin, catalyses the inactivation of cortisol (or hydrocortisone) to 6β-hydroxycortisol [15]. Following the description of various cases of rifampicin-induced adrenal crisis [16–18], certain endocrinological guidelines go so far as to recommend increasing the dose of hydrocortisone when initiating rifampicin in patients suffering from adrenocortical insufficiency [19]. While the context of intense and prolonged infectious stress raises ACTH levels and lowers CBG levels, the expected rise in cortisol is damped following induction of CYP3A4 by rifampicin. 11β-hydroxylase, under the primary control of ACTH, produces both cortisol and corticosterone, whereas aldosterone synthase, which converts corticosterone to aldosterone, is under the control of kalemia and angiotensin II [11, 20, 21]. Corticosterone not bound to CBG has been demonstrated to possess a mineralocorticoid function, albeit less significant than that of aldosterone [20]. In our case, the production of corticosterone could be increased by excessive secretion of ACTH, which could be linked both to the context of persistent stress and the enhanced degradation of cortisol by CYP3A4 induced by rifampicin. This increased corticosterone production could be associated with a decrease in its degradation due to a blockage of its transformation into aldosterone by hypokalemia and the intake of renin-angiotensin system inhibitors. This could therefore explain a new form of pseudohyperaldosteronism corticosterone-dependent favoured by rifampicin. Unfortunately, serum corticosterone is not measured in our hospital. It should be noted that an increase in serum corticosterone levels has been described in infected mice treated with rifampicin-doxycycline compared with untreated infected mice [22].

Finally, a randomized placebo-controlled cross-over trial provided direct evidence of rifampicin hypertensive effect (systolic and diastolic) in healthy humans [23]. This was confirmed with a larger trial population with rifampicin as well as in a rat model using another pregnane X receptor (PXR) agonist [24]. Both these studies

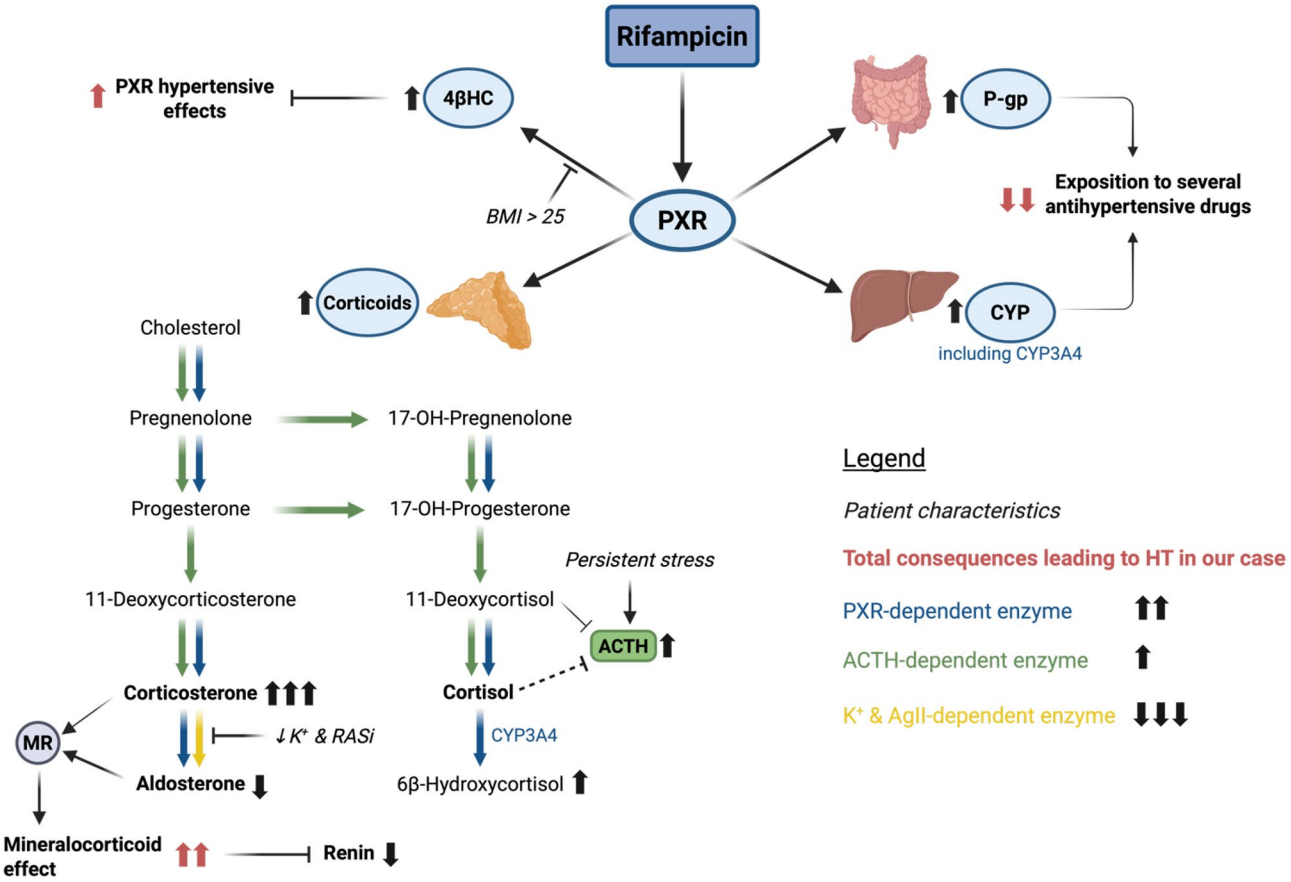

Fig. 1 Hypertensive effects of Rifampicin [10, 11, 15, 20–27]. *On the top*: rifampicin activates PXR. PXR agonism leads to hypertensive effects especially in overweight and obese patients, induction of CYP and intestinal P-gp associated with reduced exposition to several antihypertensive drugs, and increased steroidogenesis. *On the underside*: mineralocorticoid and glucocorticoid anabolism is boosted by four enzymes overexpression, including 11β-hydroxylase and aldosterone synthase. Rifampicin/PXR-induced CYP3A4 converts cortisol into inactive 6β-hydroxycortisol, decreasing the negative feedback on ACTH production. Aldosterone synthase activity is decreased during hypokalemia and under RASi, accumulating corticosterone whose synthesis depends on ACTH and PXR agonism. (4βHC: 4β-hydroxycholesterol; ACTH: adrenocorticotropic hormone; AgII: Angiotensin II; BMI: body mass index; CYP: cytochrome P450; MR: mineralocorticoid receptor; P-gp: P-glycoprotein; PXR: pregnane X receptor; RASi: renin angiotensin system inhibitors)

aimed to evaluate the role of the PXR and the serum 4β-hydroxycholesterol (4βHC) in HT [23, 24]. PXR is a ligand-activated transcription factor notably activated by rifampicin and highly expressed in liver and intestine [25]. PXR exerts broad implication in human physiology, among which a critical role in drug-associated CYP and P-gp induction (notably by rifampicin), and activation of adrenal steroidogenic enzymes [25, 26]. Pharmacological and genetic activation of PXR were associated with a severe disruption in glucocorticoid and mineralocorticoid homeostasis in mice, with high corticosterone and aldosterone levels in a ACTH-independent way [26]. The 4βHC is a cholesterol metabolite which serum level increases during CYP3A4 induction, notably during PXR activation by rifampicin [23, 24, 27]. In both human and rat models, the PXR activation led to HT and increase in 4βHC levels that was negatively correlated with the magnitude of HT, providing a negative feedback to hypertensive PXR effect [23, 24]. Serum 4βHC levels are also significantly lower in patients with a BMI >25 mg/kg², thus providing less protection against the hypertensive effects of PXR [24]. Agonism of PXR could therefore participate to a pseudo-hyperaldosteronism and explain the direct hypertensive effect of rifampicin, particularly in overweight persons, as is observed in our patient (Fig. 1).

In conclusion, this case illustrates a pattern of malignant and resistant HT consistent with the introduction of rifampicin. The use of rifampicin in previously hypertensive patients for extended periods is common worldwide. The modification of antihypertensive treatment for interaction-free molecules with rifampicin may prove critical for BP control in these conditions. However, cases of severe HT unresponsive to these therapeutic modifications have been reported, suggesting other hypertensive effects of rifampicin. This could involve as central pathway the activation of PXR by rifampicin and a corticosterone-dependent pseudohyperaldosteronism.

Abbreviations

4βHC	4β-hydroxycholesterol
ACTH	Adrenocorticotropic hormone
ARB	Angiotensin II receptor blocker
BMI	Body mass index
BP	Blood pressure
CBG	Corticosteroid-binding globulin
CCB	Calcium channel blocker
CYP	Cytochrome P450
HT	Arterial hypertension
P-gp	P-glycoprotein
PXR	Pregnane X receptor

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Author contributions
SA collected clinical data and drafted the manuscript. HJ contributed to clinical analysis and manuscript revision. All authors read and approved the final manuscript.

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Data availability
All data and materials related to this case report are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Informed consent for publication of clinical details was obtained from the patient.

Competing interests
The authors declare no competing interests.

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