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CLINICAL COMMUNICATION

Coexistence of two causes of secondary hypertension in a single patient

Coexistencia de dos causas de hipertensión arterial secundaria en un mismo paciente

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Introduction

The prevalence of secondary hypertension (SHT) is 4.7–6% in patients with arterial hypertension that are referred to specialist care settings.[1] Diagnosis is desirable, because these types of hypertension are many times resolved. It is uncommon to find two secondary causes simultaneously in the same patient. In a study performed with 1090 patients referred to a clinical unit, Omura et al.[2] found that the prevalence was slightly higher than that previously reported (93 patients with SHT). They found that primary hyperaldosteronism (PHA) was the most frequent etiology, followed by Cushing's syndrome. Of note, none of those patients had more than one secondary cause.

Here, we report a patient who had two secondary etiologies of hypertension diagnosed simultaneously. Both were resolved after they were individually treated, and the patient achieved a normotensive status.

Case report

A 56-year-old woman was referred to our clinic for hypertension. She had an unremarkable medical history, except for primary hypothyroidism treated with hormonal replacement therapy. She reported no tobacco use, alcohol abuse, liquorice intake, or illegal drug consumption. Also, she did not take non-steroidal anti-inflammatory drugs. She habitually engaged in physical activity (hiking). She had entered menopause two years earlier. She had had non-proteinuric gestational hypertension in the third trimester of her last pregnancy, but after delivery, she remained normotensive without treatment.

She had been complaining of headaches for the past six months, and that resulted in a diagnosis of hypertension. Her mean blood pressure (BP), based on 24-h ambulatory BP monitoring (24 h-ABPM) was 141/88 mmHg. Her body mass index was 24.7 kg/m^2, with a waist circumference of 75 cm. The physical examination was normal. Laboratory parameters were normal, except for hypokalemia (3.1 mequiv./l). We found an elevated aldosterone-to-plasma renin activity ratio: 3495 (pmol/l)/(ng/ml/h^{-1}), without antihypertensive drugs. A Doppler-ultrasonography of the renal arteries showed data consistent with right renal artery stenosis (RAS). Treatment with ramipril (2.5 mg/day) was then initiated, and this achieved satisfactory BP control, with an office BP of 130/80 mmHg, and mean 24 h-ABPM of 125/74 (day-time 129/76, night-time 115/71 mmHg), a systolic load (24 h) of 25.0%, and a diastolic load of 22.2%.

To complete the study, we performed a MRI scan of the adrenal glands and gadolinium-enhanced MRI-angiography of the renal arteries. The results showed a right adrenal

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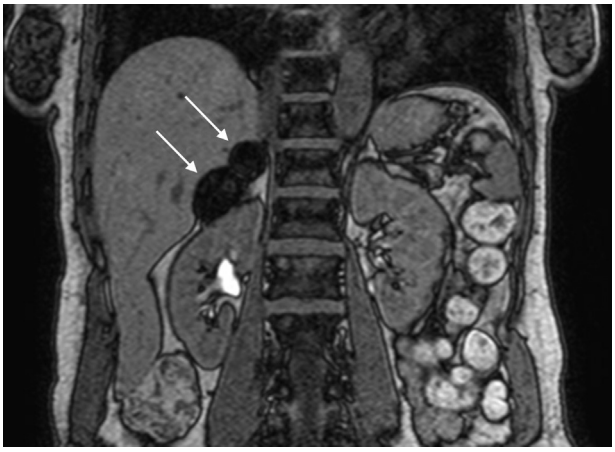

Figure 1 MRI scan of adrenal glands, showing a right adrenal mass with two adjacent nodules (21 mm × 32 mm × 26 mm and 35 mm × 32 mm × 27 mm).

mass with two adjacent nodules (21 mm × 32 mm × 26 mm and 35 mm × 32 mm × 27 mm) (Fig. 1). The right renal artery showed a feature that resembled a ''string-of-beads'', characteristic of areas of focal, concentric stenosis, alternating with small aneurysms. This affected nearly the entire course of the artery, up to the bifurcation. This finding suggested medial fibromuscular dysplasia.

Based on previous data, we performed an arteriography. It confirmed the features previously described, and the patient was treated with percutaneous transluminal angioplasty with stent placement (Fig. 2). Then, the patient underwent venous adrenal sampling with a venous catheter introduced via the femoral vein. Samples were obtained from the inferior vena cava (both above and below the adrenal veins) and from both adrenal veins. Levels of aldosterone and cortisol were measured, and the aldosterone-to-cortisol ratio was then calculated. The results were, in (pmol/l)/(nmol/l): left adrenal: 26.9/455.8 = 0.05; right adrenal: 653.83/362.3 = 1.80; vena cava above the adrenal vein: 50.22/327.7 = 0.153; and vena cava below the adrenal vein: 52.89/334.6 = 0.158.

Drug therapy was discontinued after the angioplasty. Later, a saline infusion test was performed, with no aldosterone suppression. A new 24 h-ABPM showed a mean 24-h BP of 115/67 mmHg (day-time 120/68, night-time 106/63) with a systolic load (24 h) of 1.4% and a diastolic load of 7.2%.

After the biochemical and imaging studies, a laparoscopic right adrenalectomy was performed; the histopathological study was consistent with adrenocortical adenoma. Several days after surgery, the patient underwent a 24 h-ABPM again, and the mean BP was 106/65 mmHg (day-time 109/67, night-time 100/61) with 0% systolic and diastolic loads (24 h).

Twelve months after surgery, the patient maintained normal BP measurements at home and in the office, without antihypertensive drugs (office BP 102/70 mmHg), and potassium levels had returned to normal (4.3 mequiv./l).

Discussion

PHA associated with renovascular hypertension (with subsequent secondary hyperaldosteronism) has been previously described as simultaneous causes of SHT. Most reported cases described a single patient, but the presentation showed relatively high variability among studies. Thus, although some cases were caused by fibromuscular dysplasia, most were due to atherosclerotic RAS (frequently bilateral disease). Hyperaldosteronism has been described as unilateral or bilateral, and it was associated with adrenal adenoma or hyperplasia. Those data highlighted the singularity and importance of the unusual case we described.

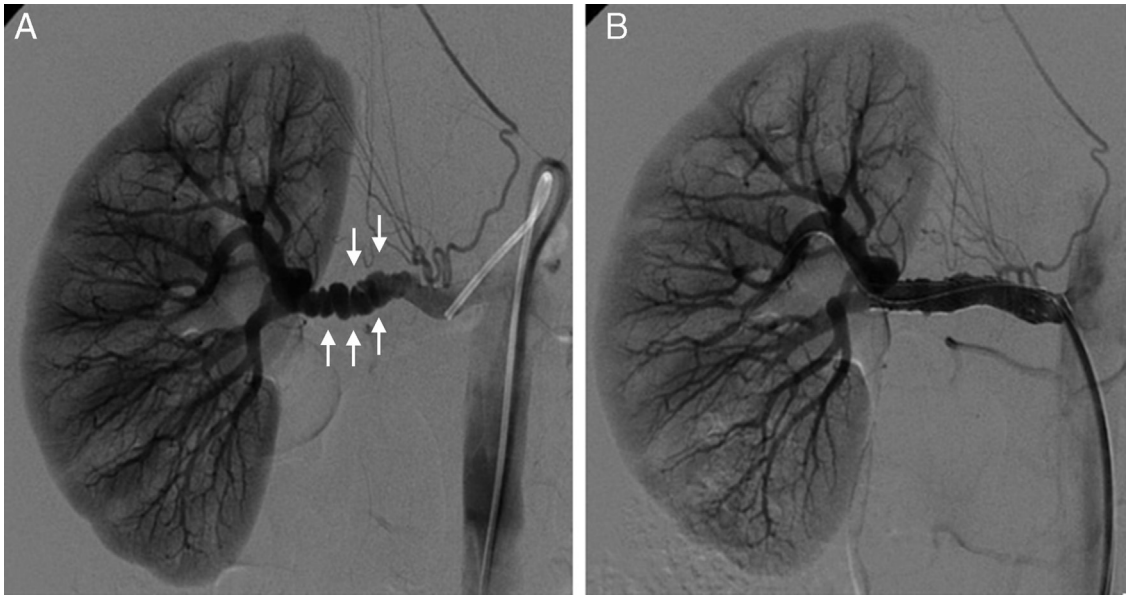

Figure 2 (A) Arteriography of the right renal artery showing a characteristic feature that resembled a ''string-of-beads'' (focal concentric stenosis alternating with small aneurysms). This affected nearly the entire course of the artery, which suggested medial fibromuscular dysplasia. (B) Treatment with percutaneous transluminal angioplasty with stent placement.

We found renovascular hypertension due to fibromuscular dysplasia and hyperaldosteronism-related adenoma, both diagnosed simultaneously.

The most similar case reported previously was that of a 22-year-old woman with severe hypertension that was diagnosed with an aldosterone-producing adenoma in the right adrenal gland. After surgery, she remained hypertensive; therefore, a more in-depth study was conducted. An arteriography showed medial fibromuscular dysplasia in her left renal artery. However, despite the treatment, she continued to exhibit mild hypertension.[3]

An association between renovascular hypertension and PHA has been described more frequently in the literature than the coexistence of other forms of SHT (e.g., Cushing's syndrome and pheochromocytoma or coarctation of the aorta, or pheochromocytoma and renovascular hypertension[4]). This has led to the theory of a tertiary hyperaldosteronism or pseudo-PHA.[5,6] This theory holds that previous renovascular hypertension, and therefore, reduced renal perfusion, could lead to increased renin secretion; in turn, this would produce secondary hyperaldosteronism. When this condition is maintained over time, the resulting enhanced stimulation of the adrenal zona glomerulosa could lead to the development of adrenal bilateral hyperplasia or adenoma, which would then produce aldosterone autonomously. However, a major objection to this theory is that no study has demonstrated the preexistence of RAS prior to the hyperaldosteronism.

Importantly, unlike other reported cases, in this study, both secondary causes of hypertension were diagnosed at the same time. In this particular case, we had to assess whether both diseases should be treated at once, or instead, whether we should start treating only one condition, and if so, which one? We decided to treat the RAS with angiography first, because during that treatment, we could assess the functional status of the adrenal nodules by selective adrenal venous sampling (considered the gold standard in this case).[7] The saline infusion test was conducted later to avoid the influence of elevated renin levels secondary to stenosis-induced renal hypoperfusion. Finally, despite achieving BP control after the first procedure, we decided to perform the adrenalectomy, because aldosterone levels had not been suppressed, and previous studies have extensively described the association between aldosterone excess and target organ damage.[8–11]

The present case report supported the importance of considering SHT when a patient with high BP presents with other, unexplained symptoms, such as hypokalemia. In these cases, hypertension can be resolved, and the patient can maintain normotension, without the need for drug therapy. This strategy would improve the patient's future cardiovascular risk.

Conflicts of interest

All the authors state that they do not have any conflict of interest.

Author contributions

1. Conception and design of the manuscript: Drs. Stiefel and Vallejo.
2. Collection of data: all authors.
3. Analysis and interpretation of the data: all authors.
4. Drafting, review and approval of the submitted manuscript: all authors.

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