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Paroxysmal hypertension due to baroreflex failure

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CASE PRESENTATION

A 78-year-old Caucasian male was referred to our hypertension clinic in February 2005 for severe blood pressure (BP) lability. He had a diagnosis of hypertension for about 10 years, but had been previously well controlled. Over the preceding 14 months, he had noticed fluctuations in BP that became progressively more severe. Based on self-monitored home BP readings, he reported systolic BP peaks of 220–240 mmHg and systolic BP nadirs of 80–90 mmHg, often happening within the same day. He also described that the rise in BP was associated with significant diaphoresis of the head and palms and facial flushing, analogous to a 'thermometer rising inside his face and head'. Occasionally he also experienced palpitations. He had erectile dysfunction but no history of urinary incontinence or retention, or any other genitourinary complaints. He had no other cardiopulmonary, digestive, neurological or psychiatric symptoms. At the time of the initial visit, his hypertension was managed with labetalol 50 mg that he took irregularly, on average once daily. In the past, he had experienced symptomatic hypotension and fatigue with diltiazem, metoprolol, and diuretics. He did not abuse alcohol or any illicit substances and did not use any over-the-counter medications or nutriceuticals.

In addition to hypertension, he had a history of squamous cell carcinoma of the left pyriform sinus (treated with extensive radiation to the neck and chemotherapy in 1998), coronary artery disease (coronary artery bypass grafting in 2000), nonproteinuric chronic kidney disease stage 3 (clinically presumed to be due to hypertensive nephrosclerosis), gastroesophageal reflux, and well-controlled hypothyroidism. In addition to labetalol, his medications included aspirin, levothyroxine, lovastatin, omeprazole, and fish oil.

On examination, the patient appeared well and calm. BP averaged 184/84 mmHg in the supine position, 152/78 mmHg when seated, and 140/74 mmHg after 5 min of orthostasis. His heart rate was 68 b.p.m. and there were no changes with posture. Fundoscopic examination revealed arteriolar narrowing and occasional abnormal arteriovenous crossings. The skin overlying his neck was taut from previous radiation exposure. There was no jugular venous distension at 30 degrees. Bilateral carotid bruits were heard; carotid pulsations were normal. Examination of the heart, lungs, abdomen, and extremities were normal. The neurological examination showed normal focused sensory and motor examination, without any Parkinsonian or cerebellar features.

Laboratory tests were significant for an elevated serum creatinine (1.9 mg dl^{-1}), with an associated estimated glomerular filtration rate of 38 ml per min per 1.73 m^2. Relevant laboratory tests, all of which were unremarkable, are listed in Table 1. A renal sonogram was unremarkable. A renal magnetic resonance angiogram was normal. Duplex ultrasound of the carotid arteries revealed hemodynamically significant bilateral carotid stenosis, confirmed by magnetic resonance angiography. A magnetic resonance scan of his brain was remarkable only for deep white matter ischemic lesions; there was no evidence of a brain stem lesion or infarct.

Owing to the patient's history of neck irradiation and clinical presentation, bedside evaluation of baroreflex pathway integrity was performed after he had been off antihypertensive drugs for 5 days. BP averaged 158/72 mmHg in the supine position, 158/64 mmHg when seated, and 156/80 in standing. The heart rate was 84 b.p.m. in all positions. The RR interval was unchanged (0.63 s) during slow deep breathing and throughout the Valsalva maneuver. We did not use a beat-to-beat monitor, so we were unable to assess the BP response to the Valsalva maneuver. The cold pressor test (hand/forearm immersion) showed an unexpected response: he had a decline in both heart rate (93–70 b.p.m.) and BP (154/78–98/60 mmHg), both of which recovered to baseline levels after 5 min of monitoring. His 24 h ambulatory BP monitoring is displayed in Figure 1, demonstrating marked BP lability.

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Table 1 | Relevant laboratory test results

Creatinine	1.9 mg dl^{-1}	PTH	52.5 pg ml^{-1}
Urea nitrogen	25 mg dl^{-1}	TSH	3.64 μIU ml^{-1}
Estimated GFR	38 ml per min per 1.73 m^2	Plasma metanephrines (total)	305 pg ml^{-1}
Sodium	139 mmol l^{-1}	24-h urine catecholamines[a]	
Potassium	3.9 mmol l^{-1}	Epinephrine (per 24 h)	<2 μg, 7 μg, <2 μg
Bicarbonate	27 mmol l^{-1}	Norepinephrine (per 24 h)	23 μg, 23 μg, 47 μg
Chloride	103 mmol l^{-1}	Metanephrines (per 24 h)	66 μg, 170 μg, 165 μg
Calcium	9.2 mg dl^{-1}	Nor-metanephrines (per 24 h)	244 μg, 233 μg, 383 μg
Phosphorus	2.5 mg dl^{-1}	VMA (per 24 h)	5.9 mg, 4.3 mg, 8.3 mg
Albumin	4.2 mg dl^{-1}	Dopamine (per 24 h)	124 μg, 146 μg, 173 μg
WBC	8,900 μl^{-1}	Plasma renin activity	2.1 ng ml^{-1} h^{-1}
Hemoglobin	14.4 g dl^{-1}	Serum aldosterone	7 ng dl^{-1}
MCV	95 fl		
Platelets	262 000 μl^{-1}		

GFR, glomerular filtration rate (modification of diet in renal disease equation); MCV, mean corpuscular volume; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone; VMA, vanillylmandelic acid; WBC, white blood cell count.
[a]Urine catecholamine profile was collected on three separate occasions. Values are listed in sequence for each of the collections.

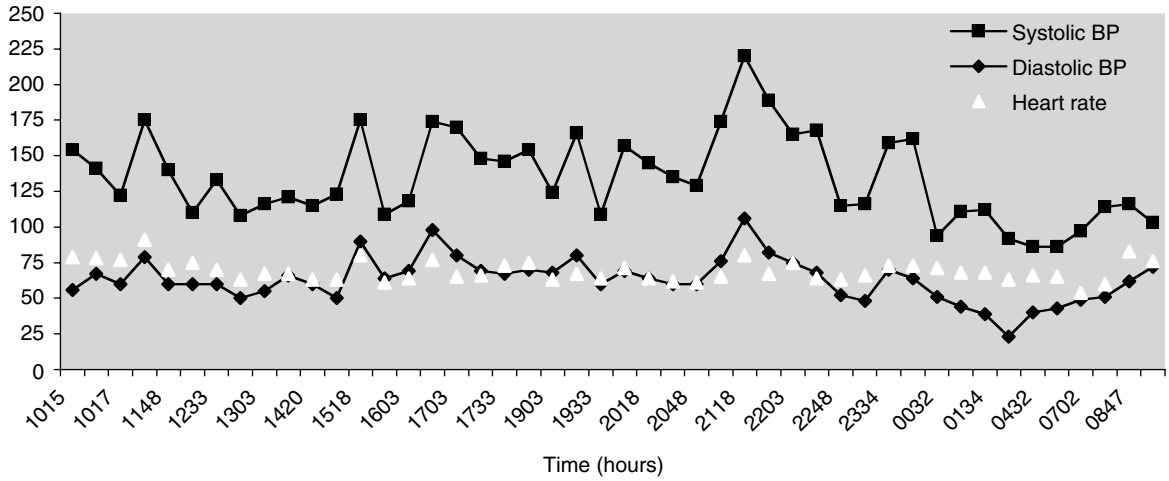

Figure 1 | Twenty-four-hour ambulatory BP recording. Average 24 h BP 110/51 mmHg (heart rate 73 b.p.m.); BP 115/54 mmHg (heart rate 74 b.p.m.) when awake, BP 98/44 mmHg (heart rate 73 b.p.m.) when asleep. Notice the highly variable BP with sudden pressor and depressor episodes with blunted heart rate variability (corroborated by the 24 h standard deviations were 30 mmHg for systolic BP, 15 mmHg for diastolic BP, and 7 b.p.m. for heart rate). The patient slept from 2330 to 0700 hours.

Clinical diagnosis

We interpreted his presentation as consistent with the syndrome of baroreflex failure as a result of previous radiation therapy to the neck.

Clinical follow-up

In the following months, the patient was tried on multiple antihypertensive regimens including α-methyldopa, lisinopril, and hydrochlorothiazine. Similar to labetalol and metoprolol, these drugs were associated with more marked hypotensive episodes and still unchanged hypertensive peaks. We repeatedly offered him a trial of transdermal clonidine, but he refused it with concerns about intolerance, which he experienced with α-methyldopa. The regimen that ultimately proved to best suit him was low-dose felodipine (2.5 mg) used 'as-needed'—he takes it about 2–3 times a week. In September 2005, he underwent bilateral carotid artery stenting. This intervention did not have any effect on his clinical behavior. He continues to have extremely labile BP by home self-monitoring, also confirmed by repeat 24 h ambulatory BP recordings.

DISCUSSION

Paroxysmal hypertension is a difficult clinical problem that often leads general internists to seek consultation from hypertension specialists, including nephrologists. The evaluation of paroxysmal hypertension demands a systematic approach to rule out the causes listed in Table 2.[1,2] In the case described, we effectively eliminated these possible causes, with a special focus on pheochromocytoma, renal artery stenosis, and a central nervous system lesion involving the brain stem. We ultimately ascribed the lability of his BP to baroreflex failure due to his previous neck irradiation. Although uncommon (two patients in a large series of 688 patients with paroxysmal hypertension[2]), baroreflex failure is an important etiology to consider, given its unique