

Case Report

Hot flushes, hypertension and haemodialysis

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Abstract

Hypertension is common in patients with end stage renal disease. However, in patients non-responsive to standard measures to control the blood pressure, non-renal causes should be considered. We present the case of a patient on haemodialysis with difficult to control blood pressure.

Keywords: end-stage renal disease; hypertension; paraganglioma

Introduction

Hypertension is common in patients with end-stage renal disease (ESRD) with retention of salt and water and activation of the sympathetic nervous system key factors. The management of hypertension in patients on dialysis typically requires a combination of lifestyle modification, careful assessment of the 'dry weight' and an increase in the duration or frequency of dialysis where possible. If these measures are ineffective, then anti-hypertensive medications are added. We present the case of a patient with difficult-to-control blood pressure (BP) which did not respond to standard therapy.

Case report

A 41-year-old Chinese man was first referred to the renal unit in August 2004 with chronic kidney disease (CKD) III. He was noted to have a body mass index of 35, hypertension, impaired glucose metabolism, heavy proteinuria and no retinopathy. Hepatitis serology, autoimmune serology and a myeloma screen were negative. An ultrasound of the renal tract showed normal-sized kidneys and no other abnormality. The cause of his ESRD was deemed to be uncertain. Despite escalating therapy for his BP and blood glucose, he had progressive renal impairment and commenced dialysis in August 2009.

On assessment, at the initiation of dialysis, his weight was 101.7 kg and he had a BP of 200/100 mmHg despite therapy with metoprolol 95 mg, cilazapril 5 mg, chlorthalidone 12.5 mg and amlodipine 10 mg daily. He had started insulin in April 2008 and was on humulin insulin 80 units

daily with a haemoglobin (Hb) A1c of 8.4. Amlodipine, chlorthalidone and cilazapril were halted. He commenced training to perform dialysis three times a week using a right radiocephalic arteriovenous fistula (AVF), dialysing for 4 h each session using an FX60 membrane. He was given dietary advice about salt and water restriction and his target weight was progressively reduced to 95 kg. His BP remained difficult to control, so anti-hypertensive agents were progressively introduced: furosemide 250 mg, metoprolol 190 mg and cilazapril 5 mg daily. Haemodialysis was increased to four sessions a week of 4.5 h.

He had been investigated for chest pains and palpitations by a cardiologist in March 2009 when he was reassured after a normal exercise tolerance test and a review with a 12-lead electrocardiogram. In December 2009, he described new symptoms including light-headedness, headache, hot flushes and sweating that usually came on after dialysis. It was noted that his systolic BP rose to 180–200 mmHg midway through dialysis with a significant fall post-dialysis on one occasion requiring infusion of normal saline. Because of his refractory hypertension and new symptoms, he was investigated for a possible pheochromocytoma. Plasma-free metadrenalines showed marked elevation of plasma normetadrenaline of 25 506 pmol/L (normal <900 pmol/L), and a mild elevation of plasma metadrenaline of 892 pmol/L (normal <500 pmol/L) as measured by enzyme immunoassay (LDN Labor Diagnostika Nord GmbH & Co.KG). A magnetic resonance imaging showed a 7.5-cm extra-adrenal mass (Figure 1).

The patient was treated with the long-acting alpha antagonist phenoxybenzamine 60 mg daily, doxazosin 8 mg daily, diltiazem 360 mg daily and metoprolol 47.5 mg daily; his target weight remained at 95 kg. He was admitted for surgery in February 2010 but was found to have uncontrolled hypertension 170/100 mmHg with a postural drop. Intravenous phentolamine was administered and his systolic BP immediately fell by 30 mmHg. The anti-hypertensive therapy was further escalated; with phenoxybenzamine 180 mg daily, doxazosin 32 mg daily, diltiazem 360 mg daily and metoprolol 95 mg daily and his target weight increased to 98 kg adequate BP control, 150/90 mmHg was achieved, without postural hypotension. The

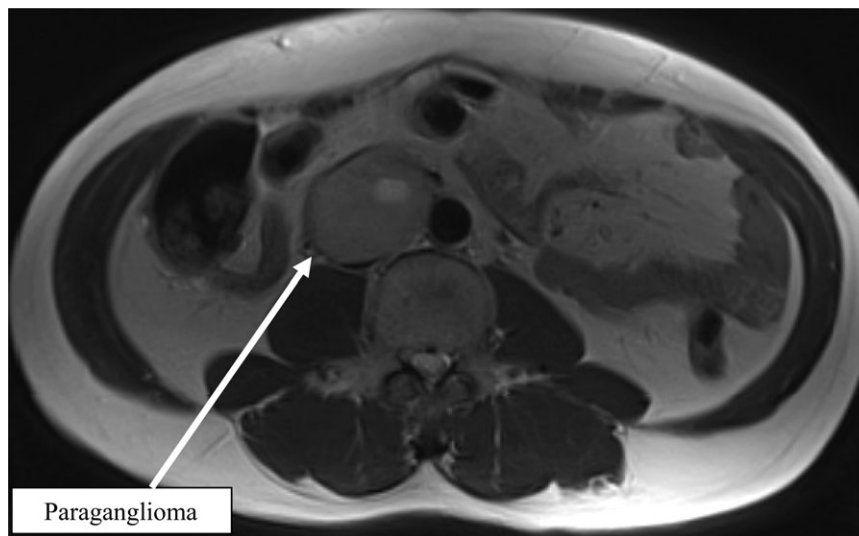


Fig. 1. A magnetic resonance imaging of the abdomen shows a high T2 signal para-aortic retroperitoneal mass that compresses the inferior vena cava inferiorly. The white area represents central necrosis.

patient went forward to an uncomplicated open excision of a large encapsulated paraganglioma in March 2010.

Two months after the operation, the patient's BP was 112/60 mmHg with no postural drop in BP, on metoprolol 47.5 mg daily at a target weight of 98 kg. The repeat investigations from May 2010 showed normetadrenaline 1782 pmol/L and metadrenaline 535 pmol/L, now both <2-fold elevated. The patient described episodes of symptomatic hypoglycaemia, so insulin was withdrawn. In July 2010, off all diabetic medications, his fasting blood sugar was found to be 6.1 mmol/L and his HbA1c 6.6%.

The patient underwent mutation analysis that showed a pathogenic autosomal dominant von-Hippel–Lindau (VHL) germline splice site mutation, c.340+5G → G-C (intronic) in IVS1. He had no family history or clinical manifestations of VHL syndrome. The patient had genetic counselling and we recommended screening for the family. The patient's daughter was identified as a carrier and will undergo further evaluation and regular monitoring.

Discussion

Catecholamine-secreting tumours occur in <0.2% of patients with hypertension [1]. The diagnosis is presently best confirmed by measurement of urine and plasma metanephrines. In patients with ESRD, urinary measurements are invalid but measurement of plasma metadrenalines indicates that a modified range for renal failure is valid with values up to 2-fold the upper limit of normal being found due to renal failure alone [2]. Our patient's initial normetadrenaline level was >25 times normal. Following surgery, the repeat normetadrenaline and metadrenaline levels remained <2-fold raised. Secreting pheochromocytoma, or paraganglioma in VHL syndrome, typically hypersecretes only noradrenaline. However, it is not unusual to require revised reference ranges for hormone analytes in patients with renal failure; a revised reference range is

recommended in relation to the interpretation of raised calcitonin values [3].

Paroxysmal hypertension is seen in half of the patients with catecholamine-secreting tumours with the rest having sustained hypertension. Episodic symptoms related to procedures have also been described and are an important clinical clue. Interestingly, our patient had paroxysms of symptoms suggestive of catecholamine release and worsening of BP through the dialysis session. Blood was drawn during dialysis to determine the serum-free metanephrines level, following a symptomatic episode.

Our patient had an extremely high level of circulating noradrenaline. Similar levels have been described in other patients with catecholamine-secreting tumours with ESRD [4]. This is probably due to both hypersecretion and reduced renal clearance. Catecholamines act on alpha- and beta-adrenergic receptors, and in cases of catecholamine excess, there is chronic constriction of the arterial and venous circulation causing hypertension. There is also naturesis and often an overall reduction in plasma volume; postural hypotension develops from an inability to further vasoconstrict the vascular beds. In our patient, we advised salt restriction, fluid restriction and removal of fluid on dialysis, standard manoeuvres to control the BP. However, in this patient each of these was likely to exacerbate the postural drop in the BP in a chronic constricted vascular system. The unusually high normetadrenaline levels were matched by the need for very high doses of alpha-adrenergic blocking drugs. Use of intravenous phentolamine identified that the patient had inadequate alpha blockade, thus the dose of phenoxybenzamine and doxazosin was progressively increased, while the target weight was increased to prevent postural hypotension. This resulted in adequate BP control in preparation for surgery.

Abnormalities in carbohydrate metabolism due to catecholamine excess such as impaired glucose tolerance or type 2 diabetes mellitus are common and are known to resolve after surgery [5] but frank resolution of overt diabetes mellitus is unusual. In our patient, we were able

to withdraw insulin and achieve satisfactory blood sugar control without drug therapy. This raises the question as to the duration of the paraganglioma and whether it may have been functionally significant from the initial assessment.

Up to 30% of patients with an apparently sporadic secretory pheochromocytoma or paraganglioma may have an inherited disorder due to a germline mutation in one of several susceptibility genes [6]. Mutations in the VHL tumour suppressor gene, the RET proto-oncogene and the succinate dehydrogenase subunit genes should be sought. Our patient underwent mutation analysis that showed a pathogenic autosomal dominant mutation. The patient has no family history or clinical manifestations of VHL [7] and thus best fits a subset of VHL syndrome of pheochromocytoma without additional VHL manifestations [8]. Pheochromocytoma occurs in ~10% of patients with VHL. These tumours typically secrete noradrenaline only and are often small, intra-adrenal and bilateral; extra-adrenal paraganglioma is rare. Although the finding of a pathologic missense mutation in the VHL gene combined with absence of other VHL manifestation suggests the presence of a pheochromocytoma phenotype, the genotype–phenotype correlation cannot be relied upon and both father and daughter will require continued surveillance for haemangioblastomas, retinal lesions and renal cell carcinoma.

Conclusions

Hypertension is common in patients with ESRD. In patients who are refractory to standard measures to control the BP, plasma metadrenalines should be measured as a screen for pheochromocytoma.

Teaching points

- (1) Catecholamine-producing tumours are a rare cause of hypertension. Clues to further investigation are severe refractory hypertension, the onset of paroxysmal turns during and after a dialysis session and worsening postural hypotension with standard manoeuvres to control the BP.
- (2) Plasma metadrenaline using a modified 2-fold higher reference range in ESRD is the best way to confirm the suspicion of a secretory tumour.
- (3) The combination of hypersecretion and reduced renal clearance may result in very high levels of catecholamine in patients on dialysis. High-dose competitive alpha blockade and increase in the target weight may be required in preparation for surgery.
- (4) Up to 30% of patients with an apparently sporadic pheochromocytoma or paraganglioma may have a germline mutation in a susceptibility gene and require screening. If pathogenic mutations are found, assessment in family members should be performed to identify at risk patients who can then undergo early screening and treatment.

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Conflict of interest statement. None declared.

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