Metastatic paraganglioma: management of orthostatic hypotension – a case report

Andrew Roberton • Albert Ferro

Department of Clinical Pharmacology, King's College London and Guy's and St Thomas' NHS Foundation Trust, London, UK

Correspondence to: Albert Ferro. Email: albert.ferro@kcl.ac.uk

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Metastatic paragangliomas are rare tumours, which characteristically secrete high levels of catecholamines, thereby giving rise to symptoms such as headaches, palpitations and profuse sweating. Orthostatic hypotension also results from these types of tumours, however the aetiology of this remains unclear. Here we describe a 40 year old lady with metastatic paraganglioma whose initial diagnosis was made at age 10. Following surgical resection and radioactive ablation, the tumour recurred in later life and she developed severely debilitating orthostatic hypotension, rendering her virtually bed-bound. We present our experience of her in- and out- patient management, balancing the need to control life-threatening blood pressure surges with that to minimize worsening of orthostatic hypotension.

Introduction

Paragangliomas, also referred to as extra-adrenal phaeochromocytomas, are neoplasms of extra-adrenal chromaffin tissue which synthesise cathecholamines.[1] The increased production and release of catecholamines causes symptoms as a result of excess alpha- and beta-adrenoceptor stimulation. These may include headaches, palpitations and profuse sweating. On examination hypertension and tachycardia may be present, although these can be paroxysmal.[2]

Chromaffin cell tumours are extremely rare, and about 5–10% of these comprise paragangliomas located in the para-aortic sympathetic chains or the urinary bladder; least commonly, paragangliomas are found in the thoracic or head and neck regions.[3] Although most commonly benign, they can occasionally (approximately 3% of paragangliomas) be malignant, with either local invasion (gross or microscopic), seen at the time of primary resection, or distant metastatic spread, which is usually only recognised at tumour recurrence.[4]

Malignant disease can often be successfully managed with high-dose radiolabelled metaiodobenzylguanidine (MIBG)[5] with or without combination chemotherapy with cyclophosphamide, vincristine and dacarbazine (CVD).[6] The rarity of the disease means the evidence base of management is currently relatively poor.

Orthostatic hypotension can also be present with cathecholamine-secreting tumours.[7] It can be defined as more than 20mmHg fall in systolic blood pressure (BP) and/or more than 10mmHg fall in diastolic BP, over a 2 minute period after standing.[8] The aetiological basis of orthostatic hypotension in this context remains unclear. For some time it has been postulated that the increase in circulating catecholamines leads to depression of sympathetic vascular response, due to alpha-adrenoceptor down-regulation; reduced blood volume is also thought to be involved, as a consequence of pressure-induced natriuresis especially when hypertension is severe and paroxysmal.[9,10] It has also been proposed that sympathetic vascular modulation is involved in the aetiology.[11]

The existing literature contains reports of orthostatic hypotension in benign disease, where measures such as increased fluid and salt intake have been used with some success. However, in the rare cases of malignant disease, with or without distant metastases, very little has been described as regards how best to manage this debilitating and poorly understood symptom. Here we describe a case of in- and out-patient management of orthostatic hypotension in a patient with metastatic paraganglioma.

Case Report

A 40 year old lady with malignant metastatic paraganglioma was admitted electively to a medical ward for management of severe and incapacitating orthostatic hypotension.

Background

She had been diagnosed at the age of 10 following unsuccessful treatment of suspected migraines. She had had symptoms of severe headaches and visual disturbances associated with sweating and vomiting, and had been treated with clonidine therapy. During a visit to her general practitioner, her blood pressure was noted to be unreadably high, and she was therefore immediately sent to hospital. In hospital, chest x-ray demonstrated a right-sided paravertebral opacity, and 24 hour urine collection revealed increased catecholamine levels. She underwent thoracotomy and tumour excision, and a diagnosis of extra-adrenal phaeochromocytoma was made. She was discharged from follow-up 3 years later.

At the age of 23, she became pregnant and had debilitating morning sickness and regular urinary tract infections. At 32 weeks' gestation, a 24 hour urine collection was performed and revealed increased catecholamines once again, at which point she was admitted to hospital. Investigations, including MIBG scanning, revealed recurrence of the paravertebral mass in her chest, and a deposit in the left scapula was also noted. She was started on oral labetalol at this point. She remained in hospital until the onset of labour at 38 weeks, at which point she underwent elective Caesarean section under general anaesthesia. 3 months post-partum, she commenced the first of five cycles of intravenous MIBG therapy, the duration of treatment lasting $2\frac{1}{2}$ years in total.

Following this treatment she remained well for the next 8 years, during which time she underwent premature menopause at age 25. At age 29, with the assistance of in-vitro fertilization, she gave birth to twins, this pregnancy being eventful only by the need for Caesarean section due to breech position and hysterectomy being necessary intra-operatively due to intra-partum haemorrhage. She was subsequently commenced on hormone replacement therapy.

She remained under regular follow-up, and another 24 hour urine collection 5 years following her second pregnancy revealed increased catecholamines once again. MIBG imaging demonstrated the known lesions in the shoulder and chest, and she underwent 2 cycles of MIBG therapy, which was complicated by thrombocytopenia. Following this she underwent repeat resection of the right thoracic mass which was adherent to the lung.

After this she remained under regular follow-up and was well, with normal urinary catecholamine secretion, until three years later when 24 hour urinary cathecholamines increased again. She underwent four further cycles of MIBG therapy, however on this occasion the catecholamine response was poor and she had also developed pain in the thoracic spine, which on further investigation (including MIBG and magnetic resonance imaging) proved to be caused by spread into the vertebral column at T3. She underwent debulking surgery including vertebral reconstruction, which led to a reduction in urinary catecholamine level; however, over the course of several months her pain increased, and further investigation revealed re-growth of the debulked tumour along with multiple new lesions throughout the spine. She underwent radiotherapy to the spinal lesions and was commenced on CVD chemotherapy.

Blood pressure management

Management of blood pressure in this patient has been extremely complex, with the need to control severe blood pressure surges whilst at the same time to avoid postural drops both from the antihypertensive medications used and from the disease process itself.

Following the completion of her first cycle of CVD she developed profoundly symptomatic orthostatic hypotension requiring admission, with postural drops of 40–90mmHg in systolic BP, leaving the patient virtually bed-bound and causing severe distress. Her BP prior to this had been managed successfully with labetalol 200mg twice daily and amlodipine 5mg once daily. In hospital, she was found to be clinically dehydrated and management was initially with aggressive intravenous fluid replacement, which caused a transient improvement in both symptoms and postural BP drop. Relief of symptoms with

intravenous hydration was very short-lived however, and although clinically euvolaemic following this, her orthostatic symptoms persisted. The amlodipine dosage was reduced to 2.5mg daily and sertraline (which she had been taking for depression) was stopped. Her BP having stabilized to some degree, she was discharged, but then readmitted for recurrence of severe orthostatic hypotension associated with paroxysms of severe hypertension; on this occasion, she was liberally intravenously hydrated, amlodipine was stopped and phenoxybenzamine was commenced, titrating up to a final dose of 20mg twice daily whilst continuing labetalol 200 mg twice daily. On this regimen she improved. Although her BP surges settled, she continued to have symptomatic orthostatic hypotension. Therefore labetalol was reduced to 50mg twice daily and phenoxybenzamine to 10mg twice daily. This resulted in an improvement both in symptoms and in BP profile, with only occasional (and short-lived) paroxysms of hypertension and, although she continues to have orthostatic hypotension, this is reduced in severity and causing very little in the way of symptoms.

Conclusion

This case specifically draws attention to the difficulty in controlling symptomatic orthostatic hypotension in patients with catecholamine excess in the context of phaeochromocytoma/paraganglioma. It highlights the severity of orthostatic hypotension and the overwhelming impact it has on a patient's life. Management centres around the need to control the BP surges on the one hand whilst aiming to minimise worsening of orthostatic hypotension. Phenoxybenzamine provides alpha blockade with the aim of reducing catecholamine-induced BP surges, as well as the resultant pressure-induced natriuresis. This, combined with the dual alpha and beta blockade provided by labetalol, achieved these desired goals in this case; although orthostatic hypotension perists, it is reduced in severity and not causing symptoms. Fine titration of these medications is required to achieve the necessary balance between controlling BP surges and avoiding excessive (including orthostatic) hypotension.

Whilst the aetiology of orthostatic hypotension in this setting remains relatively poorly understood (and this is compounded by the rarity of the condition), the principles of management outlined here may improve BP profile in such patients and, importantly, afford them relief from this potentially debilitating condition.

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