Case report

Extra-adrenal pheochromocytoma—a case report of refractory hypertension

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KEY WORDS

Extra-adrenal pheochromocytoma
Pheochromocytoma
Resistant-hypertension

A B S T R A C T

There are at least 5% of all hypertensive patients whose blood pressure (BP) remains elevated despite adequate treatment. In these cases, the clinician is forced to search for a secondary cause of the chronic BP elevation. Certain environmental factors are known to induce resistant-hypertension. Additionally, there may be pseudo-resistance occurring or the patient may be suffering from a secondary form of hypertension such as renovascular or endocrinological hypertension (pheochromocytoma, Cushing's syndrome, etc.).

We report a case of extra-adrenal pheochromocytoma who was on adequate antihypertensive medications but remained refractory to treatment prior to the exact diagnosis.

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Introduction

Refractory or resistant-hypertension is conventionally defined as systolic or diastolic blood pressure (BP) that remains uncontrolled despite adequate and sustained therapy with at least three classes of antihypertensive medications and affects 5–30% of the general population with hypertension. Although, resistant-hypertension affects a minority of treated hypertensive patients, the resulting target organ damage causes a disproportionately high-risk of cardiovascular events.¹

The main reasons of hypertension being unresponsive to the standard antihypertensive treatment include incorrect diagnosis, inadequate antihypertensive drug therapy, non-compliance towards the treatment and secondary causes of hypertension.

The importance of diagnosing secondary hypertension lies in the fact that it may convert an incurable disease into a potentially curable one. Even if the underlying disease may not be curable, being able to offer disease specific treatment will often make BP control much easier.²

Case report

A 35-year-old-female was admitted with complaints of holocranial headache and vomiting since 2 days and altered mental status since 1 day. There was no history of fever, seizures, head injury, or ear discharge. The patient had a history of repeated admissions with similar complaints of headache, vomiting, and altered sensorium. During each admission, the patient had increased BP recordings, which responded to conventional antihypertensive medications. There was no history of poor drug compliance. On examination, the patient was emaciated, afebrile, and dehydrated. Her pulse rate was 110/min which was equally palpated in all four limbs without any radiofemoral, radioradial, or apex pulse deficit. Blood pressure was 190/120 mmHg without any significant variation in all four limbs. Cardiovascular examination revealed a soft apical systolic murmur without thrill. There were no signs of meningeal irritation and her fundus examination was normal. 12-lead electrocardiogram (ECG) revealed left axis deviation and sinus tachycardia. Chest radiograph was normal. Non-contrast computed tomography (CT) scan brain was also normal. Patient was treated with enalapril (iv), nitro-glycerine (iv) in emergency ward and had marked improvement of her sensorium within three hours, but with

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Figure 1 Contrast-enhanced computed tomography abdomen showing space-occupying lesions in lesser sac with central necrosis (arrow).

persistent tachycardia. Later on, she was started upon enalapril, low-dose thiazide diuretic and beta-blockers in adequate dosage. Investigations revealed haemoglobin (Hb)—9.9g%, total leucocyte count (TLC)—7600/mm³, blood urea—28mg% and serum creatinine—0.8mg%. Serum sodium and potassium were 144 and 4.4mEq/L, respectively. During her stay in the hospital, the patient also gave a history of intermittent palpitations. Her thyroid profile was normal and 2-D echocardiography revealed mild mitral regurgitation. After 48-hours of admission, patient developed recurrent vomiting with increase in her BP readings. Conventional antiemetics failed to give any relief to the patient. Ultrasonography of abdomen revealed a 3 cm × 4 cm mass, a possible lymph node near head of pancreas located retroperitoneally. Upper gastrointestinal (GI)-endoscopy was normal. The patient's vomiting subsided spontaneously within 24 hours only to recur a day later. Serum cortisol levels were normal. 24-hours urinary vanillyl mandelic acid (VMA) level was done which came out to be 78 μmol/24 hours (normal <40). Contrast-enhanced computed tomography abdomen revealed a 3 cm × 5 cm mass in lesser sac with central necrosis abutting stomach and head of pancreas (Figure 1). Contrast-enhanced computed tomography chest and pelvis were normal. Correlating clinical, biochemical and radiological findings, the diagnosis of extra-adrenal pheochromocytoma was most likely. The patient was started on phenoxybenzamine 10mg thrice daily orally and later on, metoprolol 50mg twice daily was added to the regimen. The patient had marked clinical improvement as her pulse rate normalised and her BP got controlled. Expert surgical opinion was taken and the patient underwent exploratory laparotomy with removal of the tumour. Histopathology report showed a well-encapsulated tumour comprising of cells arranged in alveolar, trabecular, solid, and pseudopapillary pattern. Cells were mildly pleomorphic with round vesicular nucleus, granular chromatin, and abundant eosinophilic granular cytoplasm. Stroma was fibrovascular with no evidence of mitosis, necrosis, capsular, or vascular invasion (Figure 2).

Four weeks after surgery, repeat urinary VMA levels were 12 μmol/24 hours (normal <40). The patient was on 50mg metoprolol/day and was entirely asymptomatic.

Figure 2 Postoperative high magnification (40×) photomicrograph of the histopathology specimen from the tumour.

Discussion

Hypertension is one of the most common diseases, affecting approximately a quarter of the population worldwide.² Secondary hypertension constitutes <5% of the causes of hypertension. However, recent studies showed a much higher prevalence.³ The most common endocrinological cause of secondary hypertension is primary hyperaldosteronism. Other causes are Cushing's syndrome, pheochromocytoma and acromegaly.²

Pheochromocytoma accounts for 0.2–0.6% of the hypertensive population.^{4–6} Diagnosis of pheochromocytoma is important as catecholamine surges can cause cardiac arrhythmias, myocardial infarction, and even sudden death. Prolonged excess levels of catecholamines can lead to cardiotoxicity (catecholamine cardiomyopathy).⁶

Pheochromocytoma follows the rule of 10, i.e. approximately 10% are bilateral, multiple, extra-adrenal, malignant, familial and occur in children.^{4,6} A small proportion are associated with genetic diseases such as MEN 2a, MEN 2b, neurofibromatosis and von Hippel-Lindau disease.^{2,5}

Typical clinical manifestations of pheochromocytoma are hypertension, headache, palpitations, and paroxysms.⁷

However, patient may present with atypical symptoms, such as nausea, vomiting, and weight loss. Hypotension may be a presenting feature of paragangliomas.⁶ As symptoms of pheochromocytoma are non-specific, a high index of suspicion is required for correct diagnosis.

Extra-adrenal pheochromocytomas are very rare (10% of all pheochromocytoma cases) and are usually seen in the second and third decades of life. There is no sex preponderance. Extra-adrenal pheochromocytomas are often multicentric and are more likely to be malignant than those of adrenal origin.^{4,8}

Extra-adrenal pheochromocytomas tend to be larger than their adrenal counterpart at the time of detection. Symptoms of extra-adrenal pheochromocytoma can be divided into those caused due to excess catecholamines (similar to adrenal pheochromocytoma) and those caused due to the location of the tumour, which can help in localising tumour site.⁴

Several biochemical tests such as plasma free catecholamines, plasma and urine metanephrines, and urinary VMA levels can be used to demonstrate a state of catecholamine excess. Measurement of plasma free norepinephrine, epinephrine, or dopamine may be helpful in localisation of the tumour, as most adrenal tumours secrete only norepinephrine, extra-adrenal tumours secrete epinephrine and paragangliomas secrete dopamine which may be responsible for hypotensive manifestations.⁶

Both anatomical and functional imaging should be carried out to determine the exact location, number of tumours and the presence of metastasis. Adrenal tumours >5 cm in diameter are more likely to metastasise.⁹ Ultrasound, CT scan, and magnetic resonance imaging (MRI) provides anatomical imaging. However, MRI is more sensitive as pheochromocytoma usually has a distinct hyperintense signal on T2 weighted imaging which helps identify extra-adrenal tumours and metastatic disease. For functional imaging, scintigraphy is most commonly done with ¹²³I- or ¹³¹I-Metaiodobenzylguanidine (MIBG). Recently, positron emission tomography (PET) scanning with (18F)-fluorodeoxyglucose (18-F-FDG), fluorine-18-L-dihydroxyphenylalanine (18F)-DOPA or (18F)-Dopamine have shown great promise. Out of these (18F)-Dopamine is best for imaging of pheochromocytoma. When both MIBG scanning and PET scanning is negative, scintigraphy may be performed with radio-labelled octreotide (Octreoscan).⁶

Meticulous pre-operative preparation of the patient with optimum alpha and beta adrenergic receptor blocking drugs is required. Correction of hypovolaemia and management of intra-operative and post-operative blood volume and blood glucose are of paramount importance.

When tumour is inoperable, alpha methyltyrosine (metirosine), which inhibits catecholamine synthesis can be used. Radiotherapy and chemotherapy have limited effectiveness in pheochromocytoma.

Extra-adrenal pheochromocytomas are more likely to recur and to metastasise than their adrenal counterparts, making lifelong follow-up with annual determinations of catecholamine production essential.^{7,9}

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