Original Article

Phaeochromocytoma: Is it that uncommon?

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Abstract

Background: Phaeochromocytoma has been described as a rare condition in the literature.

Aim: This study aims to present cases of phaeochromocytoma seen at the University of Port Harcourt Teaching Hospital (UPTH) over a period of 6 years (2003–2008).

Methods: All patients that presented with phaeochromocytoma within the study period were included in the study. Data were collected from hospital records and presented as case series.

Results: Five cases of phaeochromocytoma seen at the UPTH between 2003 and 2008 form the subject of the retrospective report. There were three males and two females, and their ages were 40, 28, 23, 37 and 11, respectively. Four of the resected specimen were benign in histology while one was malignant. Mortality was recorded in only one patient.

Conclusion: Having seen five cases of a condition that is reported as rare within a period of 5 years raises the question as to whether phaeochromocytoma is as rare as is generally recorded.

Keywords: How rare? (uncommon), phaeochromocytoma, University of Port Harcourt Teaching Hospital

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Introduction

Phaeochromocytoma is a catecholamine-secreting tumour of chromaffin cells most commonly arising from the adrenal medulla. Extra-adrenal tumours constitute about 10% of cases and are found at the following sites: Abdominal para-aortic (75%), thoracic (10%), bladder (10%) and rarely in the neck or pelvis.[1-3] It is reported as an uncommon or rare condition in literature.[1-6] The incidence is about 1–2 per million.[1,5,7] About 01%–1% of hypertensive patients have phaeochromocytoma.[1,2,5] It occurs in all races and with equal frequency in males and females.

No age is exempted, although the peak incidence is between the third and fifth decade.[2] It had been described as the '10% tumour' because it could be bilateral, multiple, extra-adrenal, familial and malignant in 10% of cases. Over the past 5 years, five cases have been seen at the University of Port Harcourt Teaching Hospital (UPTH). This has raised the question as to whether the condition is as rare as is generally reported.

Methods

All patients that presented to UPTH with phaeochromocytoma within the study period were included in the study. Data were collected from hospital records and presented as case series.

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Results

Case report 1

A 40-year-old man presented in 2003 with episodic malignant hypertension of 4 years duration inadequately controlled with antihypertensive drugs in various private hospitals. His blood pressure was 250/150 mmHg. This fluctuated and the lowest recorded on occasion was 180/150 mmHg after slow intravenous administration of 20 mg hydralazine. On suspicion, a 24-h urine vanillylmandelic acid (VMA) estimation was done and found to be elevated at 68 mmol/per 24 h (normal 3–35 mmol per day). Fasting blood sugar (FBS) levels were high and the lowest value obtained was 10.4 mmol. He was placed on glibenclamide 10 mg daily. Other laboratory findings such as haemogram, electrolytes and urea were within normal limits. An intravenous urogram showed normal function in both kidneys. An abdominal ultrasound (US) scan showed a huge tumour of the right adrenal gland measuring 9.6 cm × 10 cm. There was no report of liver metastases. He was placed on phenoxybenzamine 10 mg twice daily and later 20 mg thrice daily. Propranolol 40 mg twice daily was subsequently added to control arrhythmias. A resection of the tumour was planned, adequate premedication was given and anaesthesia induced through an intravenous propofol 200 mg and a maintenance dose of 10 mg/kg/h. Endotracheal intubation was enhanced with vecuronium 6 mg intravenously and ventilated with nitrous oxide and oxygen mixture. In view of the apparent infiltration of the right kidney by the mass, a block dissection of the mass with the right kidney was done. The blood pressure fluctuated between 80/40 and d100/60 mmHg in the immediate post-operative period and later stabilised at 110/70 mmHg after 6 h. The resected specimen measured 21 cm × 11 cm and weighed 950 g. Histopathological examination showed tumour cells with abundant basophilic cytoplasm and a prominent cell-nesting pattern (Zellballen pattern). There is evidence of capsular invasion with extension to peri-adipose tissue. Sections of liver nodules taken at the time of surgery also revealed well-demarcated subcapsular infiltrates of similar tumour cells. These features were suggestive of malignant phaeochromocytoma.

The patient was followed up for 6 months when he was found to be well and had gained weight.

Case report 2

A 28-year-old man, a petty trader, presented with severe hypertension which had been unresponsive to treatment with alpha methyldopa, amiloride/hydrochlorothiazide (Moduretic) and propranolol. The diagnosis was initially made in Lagos in the year 2000, but patient reported to the UPTH in 2003. The paroxysmal nature of the blood pressure (fluctuating between 140/90 and 300/170 mmHg) raised a suspicion of phaeochromocytoma. He had episodes of palpitations, sweating and weakness but denied any urinary symptoms. There was no family history of hypertension. On physical examination, pulse rate was 90 beats/min, no cardiomegaly or murmurs, but there was retinopathy. Serum electrolytes, urea and creatinine levels were normal. Electrocardiogram (ECG) showed P mitrale and left ventricular hypertrophy. FBS was 7.1 mmol/L, VMA level in a 24 h urine sample was 37 mmol (normal range 10–35 mmol/24 h). A repeat FBS was 8.7 mmol/L and the patient was therefore placed on tablets glibenclamide. Abdominal US scan was unhelpful, but a computerised tomographic (CT) scan revealed a left adrenal mass which was suspected to be a phaeochromocytoma.

Surgical exploration was planned, and pre-operatively patient was placed on propranolol and nifedipine as phenoxybenzamine and phentolamine were not available. The blood pressure remained high (200/120–210/160 mmHg). Pre-medication included his morning dose of antihypertensives and oral diazepam 10 mg. Anaesthesia was a combination of regional (subarachnoid block) and general with endotracheal intubation. ECG, blood pressure and pulse oximeter monitoring were continuous including the use of temperature probe. Three large bore cannulae were used for venous access, and fentanyl 50 mg was given every 15 min until the tumour was removed. The anterior (transperitoneal) approach was used, and the blood pressure crashed following the removal of the tumour. The intravenous fluid infusion was complemented by intravenous adrenaline (3 bolus doses of 0.3 mg). Adrenaline was discontinued after 24 h and blood pressure stabilised between 140/100 and 150/110 mmHg – returned to normal on tabs Minizide within 3 weeks. Histopathological examination showed polygonal cells that were arranged in a trabeculae pattern and intermingled with thin-walled sinusoids. No evidence of capsular invasion. These features were suggestive of benign pheochromocytoma. The patient was followed up for 3 months after surgery and was in good condition.

Case report 3

A 23-year-old female student has had a year's history of recurrent blackouts (worse on standing), throbbing frontal headaches, easy fatigability, tremors, palpitations and excessive sweating. She did not lose weight. In spite of treatment with methyldopa in a private clinic, her symptoms worsened and therefore presented to the UPTH in 2003.

Examination showed a healthy – looking young female (with a slim build). The pulse rate was 112/min, regular and of good volume. The blood pressure was 220/110 mmHg (supine) and 120/80 Hg (sitting). Fundoscopy revealed no abnormality. A diagnosis of hypertension probably due to renal disease or phaeochromocytoma was made.

The following investigations and results showed, haemoglobin 12.2 g/dl, erythrocyte sedimentation rate 65 mm/h Westergren (normal 0–20 mm/h), serum cholesterol 140 mmol/L (normal 6–120 mmol/L), FBS 5.6 mmol (normal 3.5–6 mmol/L) and 24 h urine vannillyl mandelic acid (VMA) 6.6 mg (normal 0.7–6.8 mg).

An ECG showed right axis deviation with inverted T waves in leads I, II, III, avl, avf and V1–V5 – all being features of ischaemia. Abdominal US scan demonstrated an echogenic mass with a cystic centre occupying the superomedial aspect of the left kidney. CT scan showed a large isodense mass anteromedial to the left kidney. A diagnosis of left adrenal phaeochromocytoma was made.

The patient was referred to University College Hospital Ibadan (at her request) where the surgical removal of the tumour was undertaken 4 months later. Histological examination of the tumour showed phaeochromocytoma of the benign variety.

She was reviewed 1 month after surgery and found to be well. Repeat ECG showed reversal of all the ischaemic changes with normalisation of axis deviation.

Case report 4

A 37-year-old nurse, married staff of the UPTH, had been on treatment for high blood pressure by the physician for about 6 months without much improvement. She had presented with a headache, palpitations and dizziness. The blood pressure ranged from 170/100 to 200/120 despite medication with amlodipine, propranolol and alpha methyldopa (aldomet). The possibility of a phaeochromocytoma was considered and a VMA done and the level found to be high (42 mmol per 24 h). An abdominal US scan suggested a mass over the upper pole of the right kidney, and this was confirmed by a CT scan.

She was placed on tablet alpha methyldopa pre-operatively as phenoxybenzamine and phentolamine were not available in the locality.

Surgery was undertaken with combined regional (epidural) and general anaesthesia – adequate monitoring was effected with pulse oximeter, ECG, blood pressure and core temperature. Intraoperatively wide fluctuations of the blood pressure were experienced, especially with manipulation of tumour and on three occasions manipulation had to be suspended for some time at the request of the anaesthetist. Before the tumour could be finally removed, the patient developed cardiac arrest. Cardiac function was later restored, but at the conclusion of the surgery, the patient could not be reversed. She was transferred to the Intensive Care Unit (ICU) where she died within 24 h post-operatively.

The resected tumour was very large and histopathological examination showed a benign lesion.

Case report 5

An 11-year-old male child presented with palpitations, easy fatigability, exercise intolerance and intermittent chest pain.

He was found to have blood pressure ranging from 150/90 to 220/150 mmHg. This aroused the suspicion of phaeochromocytoma.

VMA estimation (done in South Africa) showed very high values (61 mmol/24 h). However, both CT scan and magnetic resonance imaging (MRI) have not been able to localise the tumour. The parents have arranged to send the child to India for iodine-labelled nudide metaiodobenzylguanidine (^{123}I-MIBG).

The child was taken to India where it was possible to localise the tumour using ^{123}I-MIBG, and the tumour was subsequently removed. Histopathological examination showed features of a benign tumour. Since his return to Nigeria, the child has been well, and the blood pressure is within the normal range for his age.

Discussion

Phaeochromocytoma has always been described as a rare (uncommon) condition[1-5] with the incidence of 1–2 per million.[5,7] Moreover, it has been observed that only about 0.1%–1% of hypertensive patients will be found to have phaeochromocytoma.[1,2,5] Indeed over a 50 years period (1928–1977), an autopsy study at the Mayo Clinic showed 54 confirmed cases out of which only 13 (24%) had been diagnosed before death.[3] All the evidence point to the fact that the condition is uncommon.

Because of the rarity of phaeochromocytoma, the condition can be easily missed by the average practising medical doctor or may prove difficult to diagnose. In general, such rare conditions require a high index of suspicion to arrive at a clinical diagnosis. The diagnosis may also be missed in those cases where the blood pressure is normal or in the paroxysmal types when the blood pressure has dropped to normal level.[1,2,4]

The blood pressure is usually high and rather difficult to control with antihypertensive treatment as in the cases described. Although it has been described commonly as paroxysmal, some cases present with a sustained blood pressure.[1,2,4,8,9] On the other hand, some patients may present with normal blood pressure.[1] It is obvious from these considerations that a clinical diagnosis may be missed in some cases.

The symptomatology is variable. It may manifest with headaches, palpitations, nervousness and weight loss. Sweating, weakness, recurrent blackouts, easy fatigability and tremors may be other presenting symptoms. The condition can, therefore, be easily confused with hyperthyroid states.

Occasionally, the manifestations are non-specific and may, therefore, mimic other conditions.[5] Physical examination usually reveals a raised blood pressure varying between 140/90 and 300/170 mmHg and which is difficult to control with known common antihypertensive drugs. Fundoscopy may show retinopathy depending on the duration of the high blood pressure. The crucial step in the diagnosis of pheochromocytoma is having a high index of suspicion. It is only then that the appropriate confirmatory investigations can be embarked on.

Phaeochromocytoma can coexist with some other hereditary syndromes such as multiple endocrine neoplasia (MEN) type 2B. It is the first manifestation of MEN 2 in 1%–25% of patients.[1] The condition may, therefore, be missed if it is not the first manifestation in the remaining 75% of cases.[1] Furthermore in von Hippel–Lindau's disease, phaeochromocytoma occurs in approximately 10%–20% cases.[2]

In the cases presented, once the diagnosis was suspected the 24 h urinary VMA was determined and found to be raised but normal in case 3. As regards localisation of the lesion US scan was unhelpful in two cases including the 11-year-old boy (in whom CT scan has also been unsuccessful). CT scan was able to localise the lesion in the rest of cases. MRI is preferred over CT scan and is said to have a sensitivity of almost 100% in detecting adrenal phaeochromocytoma.[2] This was the investigative tool used to localise the tumour in the 11-year-old child. The advantages of MRI are that it does not require the use of contrast and exposure to radiation is minimal.[2] A relatively newer technique for localisation of neoplastic chromaffin tissues which involves the use of ^{123}I-MIBG has been developed recently.[1,3,5] This compound is selectively taken up by adrenergic cells. It does not only localise the tumour but can be used post-operatively to destroy any residual tumour or metastatic tumour in the liver, lung and bone.[5] This latest technological advance was not available for use in this series. The advent of this imaging technique will no doubt make it easier to diagnose and localise phaeochromocytoma and reduce the incidence of missed diagnosis. The limiting factor for the widespread use of the technique in our environment will be cost.

The definitive treatment of phaeochromocytoma is surgical resection.[2,3,5] Surgical treatment can cure about 90% of cases.[2] Pre-operatively, alpha-adrenergic blockade is instituted with drugs such as phenoxybenzamine or phentolamine which help to re-expand the plasma volume and also control hypertension and minimise blood pressure fluctuations at surgery.[5] The five patients, who had surgery with removal of the tumours, all had pre-operative blood pressure control. Three options of anaesthesia have been described for the surgery of this condition, namely, (i) regional anaesthesia alone which could be single-shot epidural, continuous epidural of subarachnoid block, (ii) general anaesthesia alone and (iii) combination of regional and general.[2,5] The combination technique of regional and general modifies the course of anaesthesia greatly such that fewer drugs are used, and a more steady haemodynamic state is achieved.[2,10]

The major problems of surgical resection of phaeochromocytoma are encountered during handling of the tumour (when massive outpouring of catecholamines causes an extreme rise in blood pressure) and immediately after removal of the tumour (when the blood pressure may crash).[2,5,8,9] Large volumes of plasma and crystalloids are given in the latter situation to maintain the blood pressure. The blood pressure surge during tumour handling can be controlled by use of bolus hydralazine. Adequate monitoring is, therefore, essential with intra-arterial blood pressure caprograph, pulse oximeter, temperature probe and ECG.

Details of five cases of phaeochromocytoma seen at the University of Port Harcourt Teaching Hospital between 2003 and 2008

Age	Sex	Year	Duration of symptom	Site of localisation	Hospital stay	Histology	Out come	Follow up	Complication
40	Male	2003	4 years	Right adrenal gland (ultrasound scan)	14 days	Malignant	Alive	6/12	Nil
28	Male	2003	2 years	Left adrenal gland (ultrasound scan) CT scan	10 days	Benign	Alive	3/12	Nil
23	Female	2003	1 year	Left adrenal gland (ultrasound scan) CT scan	14 days	Benign	Alive	4/52	Cardiac ischaemic changes reversed after surgery
37	Female	2008	1 year	Right adrenal gland (ultrasound scan)	Died 48 years	Benign	Died within 48 h post-operative		Cardiac arrest×3 intra operative cerebral anoxia could not be reversed
	Male	2008	10 months	Lower retroperitoneum (paraganglionic tissue)	7 days	Benign	Alive	2 months	Nil

CT: Computerised tomographic

The importance of intraoperative monitoring cannot be overemphasised. The third patient in this report, unfortunately, died about 36 h after surgery in the ICU, having developed severe arrhythmias culminating in cardiac arrest on three occasions during handling of a large right-sided tumour.

About 10% of phaeochromocytomas are malignant.[1-4] The majority which are benign, however, behave physiologically in a malignant and life-threatening manner.[2] There is no clear-cut distinction between benign and malignant phaeochromocytoma.[2,9] Mitotic figures with vascular invasion and cellular atypia may be found in totally benign tumours that never recur. On the other hand, apparently benign tumours without worrisome features may recur years after an initial resection.[6]

Having seen fives cases over a period of 5 years, one is tempted to ask if the condition is as rare as has been reported in the literature. There are many reasons why the condition could be easily missed. Since it is uncommon, it is more likely to be missed without a high index of suspicion. Second, some may present with normal blood pressure[1] or in those with paroxysmal disease, at a time when the blood pressure has dropped. Under these circumstances, the diagnosis may be overlooked. Third, phaeochromocytoma can occur in association with some other hereditary syndromes (like MEN type 2A 2B). When it is not the first manifestation in such situation, it may be missed. Fourth, the condition may be mistaken for a thyrotoxic state because of the clinical presentation and it is, therefore, possible that a number of cases of phaeochromocytoma are missed every now and then.

Probably, the most fundamental reason why phaeochromocytoma may be missed is because of lack basic facilities for biochemical diagnosis and localisation of the tumour. Such case may, therefore, end up being labelled as 'malignant' hypertension.

The question arising from our experience is whether the condition is that rare taking note of the various reasons that could result in a missed diagnosis. Therefore, we advocate that the government should assist health-care institutions to acquire the facilities needed to make a diagnosis.

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Conflicts of interest

There are no conflicts of interest.

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