Phaeochromocytoma in a 20-year-old Nigerian, resolving the dilemma of benignity or malignancy

Fred O. Ugwumba,[1]
Okechukwu C. Okafor,[2]
Agharighom David Okoh,[1]
Obinna Virginus Ajuzieogu[3]

[1]Urology unit, Department of Surgery; [2]Department of Morbid Anatomy; [3]Department of Anaesthesia, University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu, Enugu State, Nigeria

Abstract

Pheochromocytomas are rare tumors that present a diagnostic challenge in developing countries. They occur in the adrenal gland and as paragangliomas along the sympathetic chain. Clinical features are usually those of sustained or paroxysmal hypertension and complications thereof. Surgical extirpation remains the mainstay of treatment and is greatly facilitated by accurate pre-operative tumor localization. Pre-operative medical management with antihypertensive medication has led to significant reductions in peri-operative mortality. Determination of malignancy is difficult in the absence of obvious metastases. We present a case of left adrenal phechromocytoma that was stabilized. Adrenalectomy had a good outcome and the patient has so far been followed up for a year.

Introduction

Phechromocytomas are rare cathecholamine secreting tumors derived from the chromaffin cells of the embryonic neural crest.[1] Most arise in the adrenal medulla. Extra-adrenal paragangliomas occur wherever sympathetic nervous tissue is found. Although these tumors are similar in origin, the clinical manifestations, prognosis and management differ[2] and occurrence of pheochromocytoma in patients with hypertensive symptoms is less than 0.5%.[3]

While pheochromocytomas and abdominal paragangliomas are catecholamine-producing tumors of the sympathetic nervous system, head and neck paragangliomas are non-secreting tumors of parasympathetic origin.[4] Recent developments in clinical and molecular research on these tumor forms have significantly clarified their genetic backgrounds and challenged the view of *pheochromocytoma as the 10% rule tumor*.[4] It has been known for some time that pheochromocytomas present as a component of the familial syndromes multiple endocrine neoplasia type 2, von Hippel-Lindau disease and, rarely, neurofibromatosis type 1.[4] Germline mutations have been identified in these diseases in, respectively, the proto-oncogene *RET*, and the tumor suppressor genes *VHL* and *NF1*. More recently, germline mutations in the genes encoding succinate dehydrogenase subunit D (*SDHD*) and subunit B (*SDHB*) have been described in patients with pheochromocytomas.[4]

The current definition of a malignant pheochromocytoma is the presence of metastases,[5] although elegant attempts have been made to outline histopathological risk factors for the malignant course of these tumors.[6] We report a case of adrenal phechromocytoma in a 25-year-old man who presented with hypertension, palpitations and excessive sweating that was managed by left adrenalectomy after medical control of symptoms, and who is free from recurrence one year after surgery. We also highlight the techniques adopted in pre- and peri-operative management of hypercatecholaminemia, the difficulty in predicting malignancy or otherwise, and strategies for improving patient compliance with follow up in a developing country.

Case Report

A 25-year-old man was referred by nephrologists with recurrent episodes of palpitation and headache of two years duration. He also complained of excessive sweating that meant he had to wash 6-7 times a day. Blood pressure was 200/120 mmHg on presentation. He was started on amlodipine 10 mg die, α-methyldopa 250 mg three times a day, and ranitidine 300 mg at night for two weeks, all in tablet form. The following tests were perfomed: serum electrolytes urea and creatinine (S/E/U/Cr), chest X-ray, postero-anterior view (CXR, PA view), serum protein, lipid profile, urinalysis, full blood count (FBC), human immune deficiency virus screening (HIV screening), hepatitis B surface antigen screening (HBsAg), hepatitis C virus screening (HCV), abdominal ultrasound scan and 24 h urine assay. The results are listed in Table 1.

The abdominal ultrasound (performed on May 4, 2010) showed: a well delineable hypoechoic solid avascular mass measuring about 98×58×66 mm in the left upper quadrant of the stomach bed. The mass lies anterosuperior to the kidney. It has 3 cysts, each about 3 cm to 5 cm in diameter in the right upper pole. Its features are highly suggestive of an adrenal tumor *e.g.* pheochromocytoma. The differential diagnosis is a pancreatic tail mass. The right kidney measures 110×41 mm while the left measures 107×44 mm in size; both kidneys are normal in echopattern. Ultrasound showed the spleen, liver, pancreas, gallbladder, etc. to be normal. The heart was moderately enlarged with left ventricular predominance (cardiomegaly).

CXR performed on 05/05/2010 showed normal radiological findings; the magnetic resonance imaging (MRI) on 26/5/2010 (Figure 1) showed a T2 weighted image of an ovoid left adrenal mass measuring 96×57×65 mm with bright signal intensity in its upper aspect suggesting a cystic component.

Impression: left adrenal solid/possible cystic mass, phechromocytoma.

Further results as follows: i) Pre-operative urine: VMA 11 mg/24 h (2-7 mg/24 h); ii) Pre-operative metanephrine: 126 μg/24 h (24-96 μg/24 h); iii) Pre-operative normetanephrine: 415 μg/24 h (75-75 μg/24 h); iv) Post-operative metanephrine: 31 μg/24 h (24-96 μg/24 h); v) Post-operative normetanephrine: 81 μg/24 h (75-375 μg/24 h). These results suggested phechromocytoma and left adrenalectomy was programmed, while antihypertensives were continued until the patient was normotensive (110/60 mmg). Several pre-operative meetings were also held with the anesthetist to discuss any possible problems and find solutions. Pre-operativemeasures adopted were: intravenous normalsaline 1 L 6-hourly and liberal oral intake of fluids24 h before surgery for volume expansion. Open left adrenalectomy was then performed under epidural anesthesia (later combined with general anesthesia with cuffed endotracheal tube, and muscle relaxation because of slow onset of the former) via an extended left sub-costal incision. A much-enlarged left adrenalgland measuring 10×6×5 cm (Figure 2) andweighing 200 g was removed. After fixation it measured 9×6×3 cm (Figure 3).

Correspondence: Fred O. Ugwumba, Urology unit, Department of Surgery, University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu, Enugu State, Nigeria.
E-mail: fredugwumba@gmail.com

Key words: phaeochromocytoma, Nigerian, benign, malignant.

Received for publication: 26 September 2011.
Revision received: 7 December 2011.
Accepted for publication: 2 January 2012.

Clinics and Practice 2012; 2:e15
doi:10.4081/cp.2012.e15

No apparent involvement of regional lymph nodes, liver, bowel, pancreas or spleen was noted. A significant spike in blood pressure and pulse rate was noted on intra-operative palpation of the tumor (maximal at 220/120 mmHg and pulse rate of 196 bpm). This was managed by increasing the rate of infusion of propofol until excision was complete.

Immediately post left adrenalectomy, BP and PR were 90/54-110/70 mmHg and 84 bpm. At a joint postoperative meeting, it was agreed that the patient did not require admission to the intensive care unit and returned, therefore, to the surgical ward. Post-operative recovery was uneventful, and the patient's vital signs were assessed half hourly for the first 6 h and hourly for the next 18 h, with the patient remaining normotensive. The patient was discharged on day 7 post surgery.

Histology [hematoxylin & eosin (H&E)] showed a nested pattern, *zellballen* appearance (Figure 4), nuclear pleomorphism and hyperchromasia as shown by bizarre tumor giant cells (Figure 5).

Diagnosis was phechromocytoma with a pheochromocytoma of the adrenal gland scaled score (PASS) of 8,[6] (Table 2).

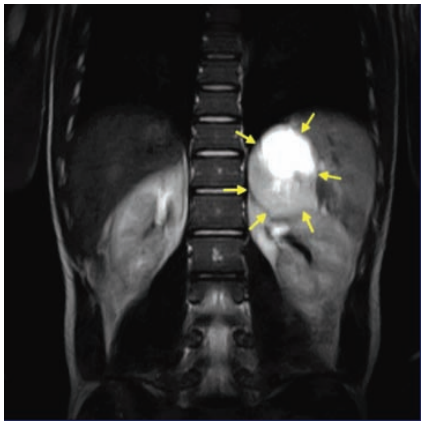

Figure 1. Magnetic resonance imaging showing the left pheochromocytoma, with tumor outlined by yellow arrows.

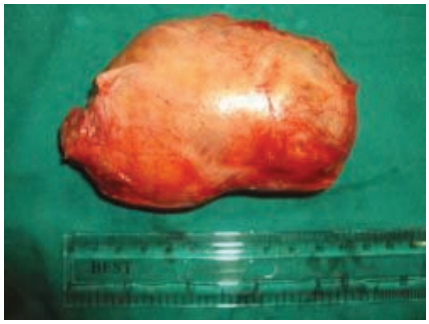

Figure 2. Pheochromocytoma immediately following excision.

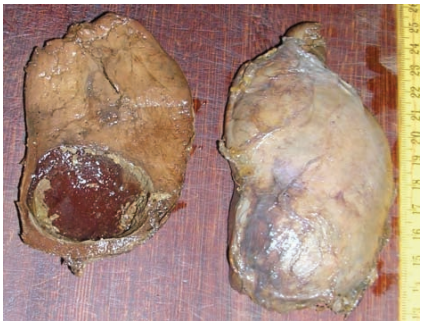

Figure 3. Pheochromocytoma fixed and split longitudinally.

Table 1. Results of tests performed.

	Results	Normal range
S/E/U/Cr		
Na^+	136 mmol/L	(135-145 mmol/L)
K^+	4.6 mmol/L	(3.5-5.0 mmol/L)
HCO_{3^-}	28 mmol/L	(24-28 mmol/L)
Cl^-	98 mmol/L	(97-108 mmol/L)
Urea	3.1 mmol/L	(2.5-8.5 mmol/L)
Cr	2.6 mmol/L	(44.2-194.5 mmol/L)
Ca_{2+}	2.6 mmol/L	(2.2-2.8 mmol/L)
PO_4^{2-}	0.8 mmol/L	(11.0-18.0 mmol/L)
Serum protein		
Total	74 g/L	(62-85 g/L)
Albumin	48 g/L	(35-50 g/L)
Globulin	26 g/L	(23-35 g/L)
Lipid profile		
Cholesterol	3.7 mmol/L	(<5.1 mmol/L)
HDL	1.7 mmol/L	(>1.5 mmol/L)
LDL	1.9 mmol/L	(<2.6 mmol/L)
VLDL	0.1 mmol/L	(>0.77 mmol/L)
TG	0.3 mmol/L	(<1.7 mmol/L)
Urinalysis*		
Appearance	Yellow and clear	
Specific gravity	Normal	
Reaction	Acid	
Protein	Nil	
Sugar	Nil	
Ketone	Nil	
Bile	Nil	
Deposits	White blood cells (WBC) 2-4 /HPF; Red blood cells (RBC) 0-1/HPF	
Casts	Nil	
Full blood count		
RBC	$4.38\times10^6/\mu L$	$(4.3\text{-}6.2\times10^6/\mu L)$
PCV	37%	(40-52%)
MCHC	32.0 g/dL	(31-35 gm/dL)
MCV	83.6 fL	(82-102 fL)
Platelets	$239\times10^3/\mu L$	$(140\text{-}450\times10^3/\mu L)$
WBC	$6.1\times10^3/\mu L$	$(4.1\text{-}10.9\times10^3/\mu L)$
Differential WBC count		
Neutrophil	39%	(35-80%)
Eosinophil	02%	(0-7%)
Basophils	01%	(0-2%)
Lymphocytes	55%	(20-50%)
Monocytes	03%	(2-12%)
Screens		
HIV1 and 2	Negative	
HBsAg	Negative	
HCV	Negative	

* Cultures yielded no bacterial growth.

Discussion

Phechromocytomas are rare cathecholamine secreting tumors derived from the chromaffin cells of the embryonic neural crest.[1] Approximately 85% arise from chromaffin cells in the adrenal medulla, and 15% arise from chromaffin tissue in extra-adrenal sites extending from the neck to the pelvis, although most are found intra-abdominally.[7] Common presenting features are hypertension, palpitations and sweating,[8] which our patient had for two years before a diagnosis was made. It has been shown that phechromocytoma is a rare tumor in black Africans with similar symptomatology to other races.[7] However, laboratory and radiological facilities for diagnosis are limited in sub-Saharan Africa.[7] A high index of suspicion remains the most important factor in determining whether a correct early diagnosis can be made.

The need for pre-operative control of blood cannot be overemphasized, as cardiovascular complications such as congestive cardiac failure, hypertensive encephalopathy and pulmonary edema are well known,[7] and it has been shown that pre-operative patient preparation has accounted for the most significant reduction in peri-operative mortality.[9]

The use of α blockade using phenoxybenzamine or prazosin to reduce blood pressure and facilitate volume expansion is well established,[9] but calcium channel blockers such as amlodipine can achieve a similar reduction without the risk of orthostatic hypotension.[10]

Access to the gland was obtained using an abbreviated chevron incision, which has been judged to provide good superior and lateral access to the adrenal gland,[10] and gave excellent exposure that allowed controlled dissection. It has been stated that, wherever possible, phechromocytoma should be removed using a laparoscopic approach, to achieve less postoperative pain, faster recovery and better cosmesis, unless the tumor is large[2] as was the case in our patient. This option was, however, not available to us at the time. We did note that the open approach afforded the patient safe and complete tumor resection.

There was no evidence of capsular or vascular invasion by the tumor, but considering the PASS score of 8,[6] we counseled the patient on the need for long-term follow up. This we have done by phone calls to remind the patient of clinic appointments and intermittent home visits to reaffirm earlier discussions regarding compliance with follow up. This was greatly facilitated by the widespread availability of cell phones in Nigeria, with the availability of global system for mobile telephony (GSM) mobile telephones since 2001.

At his last hospital visit, urine assay for metanephrine and normetanephrine were normal and repeat ultrasound showed no evidence of recurrence. We would like to perform a post-operative magnetic resonance imaging or computerized tomography, but this is not yet possible due to the cost ($450-$1000). ^{123}I-labeled meta-iodobenzylguanide scintigraphy and positron emission tomography using ^{18}F fluorodopamine are not currently available in our setting.

In conclusion, pheochromocytoma management is challenging and is made more so in countries with limited resources. It can, however, be diagnosed and treated effectively, with a high index of suspicion especially amongst primary care physicians. We recommend the following guidelines to aid diagnosis and treatment in developing countries.

In settings with few resources, all newly diagnosed hypertensive patients under the age of 35 years be screened with the following simple easily available tests: i) urine metanephrine; ii) urine normetanephrine; iii) urine Vma; iv) abdominal ultrasonography to detect presence of adrenal and or other retroperitoneal swellings; v) genetic testing (where available) for germline mutations in RET proto oncogene, *VHL* tumor suppressor gene, NF-1 tumor suppressor gene, and B and D subunits of mitochondrial succinate dehydrogenase SDHB and SDHD, under the following conditions: i) positive family history; ii) clinical evidence of syndromic disorder *e.g.* VHL and MEN 2.

Treatment: i) determine total number of swellings and trigger factors; ii) perform abdominal, MRI Scanning or CT scan if MRI is not available to localize tumor properly; iii) commence pre-treatment with calcium channel blockers; iv) avoid β blockers if possible; v) commence volume replacement on admission 24-48 h before surgery, and assess adequacy of same with urine output monitoring; vi) establish contact and have a patient-centered discussion with an anesthetic team to anticipate problems and offer solutions to them proactively and prepare for same; vii) anticipate possible intensive care unit admission pre-operatively and prepare for same.

In conclusion, the role of adequate pre-operative preparation is vital to reduce perioperative morbidity and mortality, and is safely achieved with calcium channel blockers and volume expansion using normal saline.

Open adrenalectomy offers standard care and postoperative follow up should be rigorous.

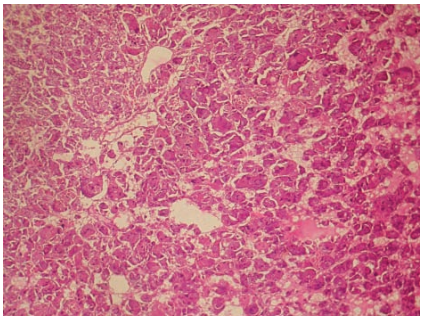

Figure 4. H&E, X150. Note the zellballen appearance with high cellularity.

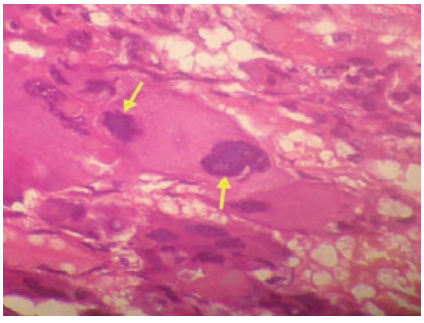

Figure 5. H&E, X600. Note the nuclear pleomorphism and hyperchromasia (yellow arrows).

Table 2. Pheochromocytoma of the adrenal gland scaled score (PASS).

Criterion assessed	Score
Vascular invasion (1)	-
Capsular invasion (1)	-
Peri-adnexal adipose tissue involvement (2)	-
Large nests or diffuse growth (2)	-
Focal or confluent necrosis (2)	-
High cellularity (2)	2
Tumor cell spindling (2)	-
Cellular monotony (2)	-
Increased mitotic figures (>3/10HPF) (2)	2
Atypical mitotic figures (2)	2
Profound nuclear pleomorphism (1)	1
Hyperchromasia (1)	1
Total	8

References

1. Frankel F. Classics in oncology. A case of bilateral completely latent adrenal tumor and concurrent nephritis with changes in the circulatory system and retinitis: Felix Frankel, 1886. CA Cancer J Clin 1984;34:93-106.
2. Adler JT, Meyer-Rochow Gy, Chen H, et al. Pheochromocytoma: current approaches and future directions. The Oncologist 2008;13:779-93.
3. Stein PP, Black HR. A simplified diagnostic approach to pheochromocytoma. A review of the literature and report of one institution's experience. Medicine (Baltimore) 1991;70:46-66.
4. Elder EE, Elder G, Larsson C. Pheo-chromocytoma and functional paraganglioma syndrome: no longer the 10% tumor. J Surg Oncol 2005; 89:193-201.
5. Alderazi Y, Yeh MW, Robinson BG, et al. Phaeochromocytoma: current concepts. Med J Aust 2005;15;183:201-4.
6. Thompson LD. Pheochromocytoma of the Adrenal gland Scaled Score (PASS) to separate benign from malignant neoplasms: a clinicopathologic and immunophenotypic study of 100 cases. Am J Surg Pathol 2002; 26:551-66.
7. Huddle KR. Phaeochromocytoma in black South Africans - a 30-year audit. S Afr J Surg 2010;48:127-31.
8. Bravo EL, Tagle R. Pheochromocytoma: state-of-the-art and future prospects. Endocr Rev 2003;24:539-53.
9. Duh QY. Evolving surgical management for patients with pheochromocytoma. J Clin Endocrinol Metab 2001;86:1477-9.
10. Ulchaker JC, Goldfarb DA, Bravo EL, Novick AC. Successful outcomes in pheochromocytoma surgery in the modern era. J Urol 1999;161:764-7.