CASE REPORT

Phaeochromocytoma in early pregnancy: A case report and review of the literature.

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Abstract
Phaeochromocytomas are rare neuroendocrine tumors of the adrenal. They are a very rare cause of secondary hypertension. They are very rare in pregnancy and much more so in early pregnancy. In this narrative review, we conducted a MEDLINE search of review articles on phaeochromocytoma from 2000 to 2018 using the key words "phaeochromocytoma, early pregnancy, hypertension, catecholamines, and chromaffin tumors. We identified relevant articles and also looked up key references. We also highlight the challenges and limitations of our management experience in our practice setting. Although phaeochromocytomas are very rare in early pregnancy, a high index of suspicion is needed to make this diagnosis. Otherwise, it may be misdiagnosed as pregnancy induced or related hypertension.

Keywords: Phaeochromocytoma, early pregnancy, hypertension, catecholamines, chromaffin tumors

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RAPPORT DE CAS

Phaéochromocytome en début de grossesse: rapport de cas et revue de la littérature.

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Resume
Les phéochromocytomes sont des tumeurs neuroendocrines rares de la surrénale. Ils sont une cause très rare d'hypertension secondaire. Ils sont très rares pendant la grossesse et beaucoup plus en début de grossesse. Dans cette revue narrative, nous avons effectué une recherche dans MEDLINE d'articles de synthèse sur le phaéochromocytome de 2000 à 2018 en utilisant les mots clés «phaeochromocytome, début de grossesse, hypertension, catécholamines et tumeurs à chromaffine. Nous avons identifié des articles pertinents et avons également recherché des références clés. Nous soulignons également les défis et les limites de notre expérience de gestion dans notre milieu de travail. Bien que les phéochromocytomes soient très rares en début de grossesse, un indice de suspicion élevé est nécessaire pour poser ce diagnostic. Sinon, il peut être mal diagnostiqué comme une hypertension liée à la grossesse ou une hypertension associée.

Mots-clés: Phaéochromocytome, grossesse précoce, hypertension, catécholamines, tumeurs chromaffines

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INTRODUCTION

Phaeochromocytomas are neuroendocrine catecholamine producing tumors (1). They occur in one or both adrenal glands, the rest occurring in the sympathetic ganglia (2). They account for 3-8 % of all incidental adrenal masses (3,4,5). Its incidence is less than 0.2 per 10,000 pregnancies (6). It has an incidence of 2-8 cases per million per year in the general population (7). The prevalence of Pheochromocytoma in hypertensive patients is about 0.2 -0.4%, however, in term pregnancies it is estimated at 0.002% (8). It is a rare but important cause of secondary hypertension in pregnancy (9). The prevalence of Phaeochromocytoma in pregnancies carried to term is 1 in 50, 000 – 54, 000 (10,11).

About one-quarter of these tumors arise from genetic mutations (10,11). Genes mutations implicated in the formation of Phaeochromocytoma include succinate dehydrogenase subunit B (SDHB) gene *and* succinate dehydrogenase subunit D (SDHD) gene, *SDHD (12)* . Some of these tumors are associated with von Hippel-Lindau (VHL) disease, multiple endocrine neoplasia type II (MEN II) and neurofibromatosis type I (13).

The clinical manifestations of these tumors are due to the array of hormones they produce: dopamine, epinephrine and norepinephrine. Norepinephrine is the dominant hormone, and is responsible for the sustained or paroxysmal hypertension with episodes of hypotension. Dopamine secreting tumors present with hypotension or normotension. Epinephrine producing tumors can cause vasodilatation and shock (14,15). In most patients, the clinical manifestations are accounted for by contributions from these three hormones (16) Phaeochromocytomas also produce ectopic hormones such as gastrin, serotonin, vasoactive intestinal peptide, adrenocorticotropic hormone, substance P, somatostatin, and calcitonin. This explains the wide array of symptomatology and also why it may pose a diagnostic challenge (117,18). Only about 50% of phaeochromocytomas are symptomatic. Most are discovered as incidental adrenal masses or are found during autopsy (19).

The purpose of this review is to describe a rare case of phaeochromocytoma seen in early pregnancy and also to review the existing literature. Finally, we highlight our management experience and the challenges we faced in our practice setting.

CASE REPORT

Mrs. F H is a 32-year-old gravida4 Para1^{+2}(1 alive) trader who was rushed in to the accident and emergency unit of the University of Port Harcourt Teaching Hospital at 13 weeks of gestation. She presented with a history of fainting attack of 12 hours duration associated with nausea and vomiting, persisting headache and generalized body weakness. She also complained of episodes of short-lasting paroxysmal palpitations and sweating. There was no history of orthopnea, paroxysmal nocturnal dyspnea or leg swelling. She had no vaginal bleeding or urinary symptoms. She was not a known hypertensive or diabetic prior to index pregnancy. One week prior to her presentation, she was admitted into the gynecological ward and was managed for threatened miscarriage. Her only confinement was 2 years prior to index pregnancy. She had emergency caesarean section for severe pre-eclampsia at 36weeks gestation with good fetal outcome. Her blood pressure had normalized prior to discharge 5 days after the delivery.

Past surgical history revealed an ovarian cystectomy which was done five years ago. Her brother died of hypertension related complications several years ago. She neither took alcohol nor tobacco in any form.

Her general physical examination was normal save for a body mass index of 26.4 kg/m^2. Cardiovascular system examination showed a tachycardia of 100/min with a blood pressure of 210/120 mmHg. Abdominal examination revealed a midline sub-umbilical scar, a fundal height of 22/52 weeks and no organomegaly. Other systems examination was normal. A provisional diagnosis of labile hypertension in pregnancy was made. Differential diagnoses considered were phaeochromocytoma; thyroid disease and molar pregnancy. Urinalysis was normal. Full blood count showed a packed cell volume of 31.0 % but other parameters were within normal limits. Serum electrolyte, urea, creatinine and uric acid were also within the normal range. Abdomino-pelvic ultrasound scan showed intrauterine singleton active fetus with good cardiac activity at 13 weeks gestation co-existing with multiple uterine fibroids. There was an iso-echoic mass closely related to the liver at the point of entry of the inferior vena cava measuring 5.9 cm by 5.2 cm diameter. Twenty four-hour urine normetanephrine was markedly elevated at 62, 984.0 nmol/24 hours (573.0 -1, 932.0 nmol/24 hours). Normetanephrine-creatinine ratio was 4,738: 1 (26 -200: 1). Serum

T3/T4 levels were normal. Magnetic resonance imaging of her abdomen was not done due to financial constraints. A definitive diagnosis of Pheochromocytoma in pregnancy was made. She was counseled on her condition, its complications and the management options.

A pointer to her diagnosis was the sudden drop in her presenting blood pressure to 80/40 mmHg, 5 minutes after administration of 20 mg of intravenous labetalol. This blood pressure drop was followed by paroxysms of fainting. At this time, she had now developed cold clammy extremities. She was resuscitated with 200ml of 0.9% normal saline over 10 minutes. Following this, her blood pressure suddenly rose to 250/130 mmHg. Intravenous fluids were thus discontinued. She was given prazosin (5mg daily), an α_1 selective blocker, and oral nifedipine (20mg daily) a calcium channel blocker. However, her blood pressure continued to fluctuate between 80/20 mmHg and 250/130 mmHg. She kept having paroxysms of severe hypertension and hypotension with syncopal attacks. A planned laparoscopic exploration was not done due to financial constraints. Her condition progressively worsened leading to medical termination of the pregnancy 6 weeks after admission. At cervical assessment, the Bishop score was 3, so intracervical extra-amniotic Foley catheter, size 18FR was passed into the uterus and retained with 50mls of sterile water for 24 hours. Repeat Bishop score after 24hours was 5 and the intracervical extra-amniotic catheter was repeated and removed after 24hours. The Bishop Score improved to 9 and she was having mild lower abdominal pain. An intravenous solution of 1Litre Normal saline with 20 units of oxytocin was commenced at 30dpm to induce an maintain intermittent uterine contractions. She received 10mg of pethidine and 25mg of promethazine for pain relief. She also continued her anti-hypertensive throughout the induction. She expelled a fetus and the placenta after 7hours of the induction. The feotus weighed 215gms. Her systolic blood pressure ranged between 160 to 180mmHg and the diastolic blood pressure between 95 to 110mmHg during the induction. The paroxysms of hypertension and hypotension with syncopal attacks reduced significantly following termination of her pregnancy. She was counseled on contraception and discharged to the Surgeons and the Endocrinologist for definitive management.

DISCUSSION

The diagnosis in the index case was made quite early at 13 weeks of gestation, due to the paroxysmal nature of her presenting symptoms and a high index of suspicion. The symptoms of phaeochromocytoma are due to excessive synthesis and release into the systemic circulation of catecholamines (20). During pregnancy complicated with phaeochromocytoma, there are transient excessive maternal levels of catecholamines which have deleterious effects on the utero-placental circulation; this may lead to extreme vasoconstriction of the vascular bed and subsequent placental abruption and intrauterine hypoxia of the fetus as sometimes seen in these patients (21). Some patients with pheochromocytoma in pregnancy may be asymptomatic. However, some may present as a life-threatening hypertensive emergency, as was the case of this patient. Features may include hypertension which may be labile, headache, excessive sweating and palpitation as was seen in our patient (22). Other reported symptoms in these patients include; persisting nausea, vomiting, generalized weakness, breathlessness and chest pain, photophobia, tinnitus, insomnia, weight loss, hyperglycemia and heat intolerance (23). Others may present with anxiety and syncopal attacks as was the case with our patient (24). Other features which may suggest pheochromocytoma are postural hypotension, congestive cardiac failure, seizures, visual disturbances and abdominal pain in pregnancy. Our patient had postural hypotension and abdominal pain.

Many pregnant patients with pheochromocytoma become increasingly symptomatic with increasing gestational age, probably due to the growing size of the uterus, movements of the fetus, uterine contractions and abdominal palpation. The diagnosis of pheochromocytoma in pregnancy is often missed because of the varied signs and symptoms that may mimic other forms of hypertension in pregnancy, including pre-eclampsia (25). Other differential diagnoses are thyrotoxicosis/thyroid storm and panic attack. Hence, in making the clinical diagnosis of pheochromocytoma in pregnancy, a high index of suspicion is required as well as carefully obtaining a good history of the symptom profile.

The diagnosis of phaeochromocytoma depends on the biochemical demonstration of excessive production of catecholamines or their

metabolites in the plasma or urine of these patients (26). The 24-hour urinary catecholamines are highly recommended in pregnancy because; pregnancy does not cause elevation of urinary catecholamine levels into the diagnostic range for pheochromocytoma (27). On the other hand, plasma metanephrines as a screening test for pheochromocytoma is said to have a poor specificity at 85% to 89% (28).

The metanephrines and normetanephrine are the O-methylated derivatives of epinephrine and norepinephrine respectively. The normal values for urinary metanephrines and normetanephrine are less than 900 µg per 24-hour urine and less than 600 µg per 24-hour urine respectively. The index patient had markedly elevated normetanephrine of 62,984.0 nmol per 24-hour urine. Other derivatives of epinephrine and norepinephrine which could be assayed as a screening test for pheochromocytoma are plasma or urine vanylmandelic acid (VMA), fractionated metanephrines, urinary dopamine which was assayed in the past, as well as normetanephrine: creatinine ratio (29,30). The normetanephrine:creatinine ratio was found to be elevated in this patient.

After biochemical confirmation of the presence of the tumor, the next step is localization of the tumor. This is done by performing an abdomino-pelvic magnetic resonance imaging (MRI) or computerized tomography (CT) scan. MRI classically shows a bright-bulb lesion on T2 comparable to the signal intensity of CSF (31). Unlike CT scan, MRI does not expose the fetus to radiation (32). CT changes range from areas of low to high attenuation (33,34). Abdominal ultrasound scan may play a role in localizing the tumor (35).

Functional imaging is indicated if abdominal imaging studies are negative. ^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG or MIBG) is the ligand commonly used for functional imaging. MIBG is a norepinephrine analog that is taken up by the presynaptic adrenergic nerves and sympathomedullary tissue before ending up finally in cytoplasmic storage vesicles by an active amine uptake system (36). The uptake of MIBG is proportional to the number of secretory granules within the tumor. Hence, the classic appearance of a pheochromocytoma is unilateral focal uptake within the tumor (37,38). Positron emission tomography PET is a diagnostic modality mostly used in research settings. It is limited by its unavailability and cost issues (39,40).

The definitive treatment of pheochromocytoma is the surgical excision of the tumor once the diagnosis is confirmed. However, the timing of surgery during pregnancy is controversial and challenging. It may depend on the gestational age at presentation, the clinical response to medical treatment, and the presence or absence of fetal distress. The management of pheochromocytoma in pregnancy is multidisciplinary and requires the collaboration of the cardiologists, endocrinologists, obstetricians, paediatricians, anesthesiologists and general surgeons to ensure the best outcome for mother and baby. We employed a multidisciplinary approach in the management of this patient.

Good foeto-maternal outcome is best achieved by perioperative optimization of the patient. Electrocardiogram, echocardiogram and a chest radiograph are mandatory in the pre-operative evaluation of these patients. Electrolytes, urea and creatinine should also be performed to assess adequacy of renal function. In addition, the control of blood pressure, the heart rate and restoration of the blood volume are very important. The aim is to prevent an acute hypertensive crisis in the operating room and reduce the risk of catecholamine-induced hemodynamic changes during anaesthesia and surgery and involves the combination of α-adrenergic blockers and β-blockers. Examples of α-adrenergic blockers commonly used are; Phenoxybenzamine, a non-selective long acting α-adrenergic blocker, and prazosin, a short acting α_1-adrenergic blocker. Dihydropyridine calcium channel blockers such as felodipine may also be used alone or in combination with the α_1-adrenergic blockers or as primary treatment of hypertension. The side effect of α-adrenergic blockers is postural hypotension (41). The calcium channel blockers induce minimal hypotension and has the advantage of causing smooth muscle relaxation in peripheral and coronary arteries, inhibiting the norepinephrine-stimulated calcium influx into vascular smooth muscles (42). Magnesium sulphate can be used for pre-operative control of blood pressure in patients with pheochromocytoma. It acts by modulating adrenergic receptor response to catecholamine and also prevents their release from the chromaffin cells (43).

The critical period of hemodynamic instability intra-operatively are; while moving the patient on the table, during induction of general anaesthesia, at initiation of mechanical ventilation due to raised intra-abdominal pressure and while directly manipulating the

tumor during surgery. During these critical periods, there's usually a surge of catecholamine release and therefore an increase in the arterial blood pressure. These however can be limited by increased anaesthetic drugs and muscle relaxation as well as careful surgical handling of the tumor (44,45). Hypertension, following pheochromocytoma removal is definitively controlled within a few hours to days (46,47). Other post-operative complications are rebound hypoglycemia secondary to excessive insulin secretion and persistent hypertension (48)

The mortality from undiagnosed phaeochromocytoma is very high, about, about 50%. Most deaths occur during induction of labour or vaginal delivery (49). Early diagnosis and prompt intervention reduce maternal and fetal mortality to <5% and <15% respectively (50,51,52).

Conflicts of interest: The authors declare no conflicts of interest.

CONCLUSION

Pheochromocytoma in early pregnancy is life-threatening to mother and foetus, may pose diagnostic, therapeutic and management dilemmas. However, a high index of suspicion, prompt diagnosis, and prompt treatment in a multidisciplinary approach may improve foeto-maternal outcomes.

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