Extra-adrenal Pheochromocytoma: Experience in Mulago Hospital.

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Exta-adrenal pheochromocytomas are rare tumors that arise from extra-adrenal chromaffin cells of the sympathetic ganglia. Experience with two cases is reported here and a review of literature was conducted. Like pheochromocytomas, extra-adrenal pheochromocytomas present with episodic hypertension, tachycardia, headache, and diaphoresis, and can be either benign or malignant. Diagnosis is made by serum and urine analysis for catecholamines and metanephrines, and confirmed with imaging studies including computed tomography scanning, magnetic resonance imaging, or 123-I metaiodobenzylguanidine imaging. Ultrasound scanning in the developing world is beneficial. Genetic testing should be offered were available, particularly patients who are young, have multiple tumors, or have a family history of malignancy. Management of extra-adrenal pheochromocytoma is enblock en-mass surgical resection. Chemotherapy, and radiation therapy may be necessary in malignant disease. Long-term follow-up is essential, as extra-adrenal pheochromocytomas can recur many years after initial diagnosis.

Introduction

Exta-adrenal pheochromocytomas are rare tumors that arise from extra-adrenal chromaffin cells. They represent 10–18% of all chromaffin tissue-related tumors[1-3]. These tumors may be divided into tumors derived from the parasympathetic or sympathetic ganglia. Most parasympathetic ganglia derived are found in the neck constituting of about 69% [4]. The common sympathetic ganglia derived tumors are found within the adrenal medulla consisting of 85-90% and are called pheochromocytoma and those that arise outside the adrenal gland are known as paragangliomas or Extra-adrenal pheochromocytoma of which the majority are found in the para-Aorta sympathetic chain, commonly located in the organ of Zuckerkandl (centered around the root of the inferior mesenteric artery)[5,6,7].

The presentation of extra-adrenal pheochromocytoma varies widely, but early recognition and appropriate treatment is necessary to avoid morbidity and potential mortality associated with the disease. Only 10% of the extra-adrenal pheochromocytomas are malignant, however, this often cannot be determined on a biochemical or histologic basis. Malignancy in these tumors is defined by the presence of local invasion on gross or microscopic examination at the time of resection, or much more commonly by the presence of metastases, which may only be recognized years later when the tumor recurs[8]. Further, in certain familial syndromes, the rate of malignancy in extra-adrenal pheochrocytomas can be as high as 50%[9].

In this article, we report our experience with two cases of extra-adrenal pheochromocytomas and review similar cases published in the literature, focusing on the clinical presentation, diagnosis, management and prognosis. For purposes of clarity we will use the term extra-adrenal tumors referring to paragangliomas.

Case reports

Case 1.

A 53-year old woman presented with 3-years history of on and off palpitations, sweating and severe headache at the heart institute. She was thought to have post-menopausal syndrome with Labile Hypertension. She developed a Hypertensive Crisis, received multiple antihypertensives (verapamil, carvedilol, enalapril, digoxin and primaan) with little improvement of the symptoms. The throbbing headache, dizziness, blurring of vision, palpitation with chest pain worsened. An abdominal ultrasound and CT revealed a retroperitoneal mass in the vicinity of the left side of abdominal aorta below the lower. The mass measured 7 X 4 cm, diagnosed as extra-adrenal pheochromocytoma from

organ of Zuckerkandl was noted. The Vanillymandellic acid (VMA) assay was normal. The patient had a recurrent thyroid nodule with normal thyroid. The patient was put on prasozin only and liberal salt intake. Propranolol was introduced after the patient remained tachycardic. The blood pressure dropped to normal ranges after 2-weeks of prasozin.

Laparatomy was performed and a mass on the left side of the abdominal aorta extending caudally from below the lower pole of the left kidney excised. Both kidneys were normal. Intraoperatively patient was stable. A yellowish brown tumor nodule measuring 7x4x4 cm, with histologically large tumor cells with granular cytoplasm and fibrovascular stroma was diagnosed.
Patient's postoperative blood pressure was normal and stable. Prasozin was stopped she was discharged, followed for 3-years with recurrence of symptoms.

Case 2.

A 12-year old boy was referred with a 2-month history of headache, abdominal pain, nausea & occasional vomiting and constipation, Palpation, Excessive sweating and generalized body weakness. He had labile blood pressure. He did not respond to conventional treatment (Atenolol, Nifedipine), and pain killers (Cetamol). Abdominal US revealed a well defined predominantly solid mass with central cystic area, anterior to the left Psoas muscle and inferior to and separated from the lower pole of left kidney. It measured 5.4 x4.6 cm. Adrenal areas were free. Laboratory evaluations at the time revealed normal 24-hour Vanillymandellic acid (MVA).

Patient received α-adrenergic blockade (parasozin) , the rest of the drugs were stopped. Patient was allowed liberal salt intake to replete the intravascular volume. Bed rest was encouraged while abdominal examination was restricted. Propranolol was re-instituted as pulse remained > 90b/min.
At laparotomy a yellowish brown tumor measuring 5 X 4 cm was excised, patient was stable. Histoloy confirmed pheochromocytoma. Postoperative urine VMA levels were normal and the symptoms resolved.

Two years after surgery the patient remains disease-free.

Discussion

Clinical presentation

Extra-adrenal pheochromocytomas cause clinical symptoms as a result of the catecholamines (epinephrine, nor epinephrine, and dopamine) that are released by the tumors. The classic triad of symptoms associated with these tumors are episodic headache, diaphoresis, and tachycardia[10,11,12]. The presentation depends primarily on whether it is of parasympathetic or sympathetic origin, although there may be an overlap between the two types. The mode of presentation may be in form of mass effect, incidental discovery or excess catecholamine production[4,13,4].

Excessive Catecholamine production is however the commonest presentation and is one of the most worrisome manifestations and can be life threatening. The classic constellation of signs and symptoms associated with catecholamine excess include headache (26%), palpitations (21%), sweating (25%), and episodic hypertension (64%)[13,4,6,14]. Only a third of the patients will present with these striking features. Other less common features associate with catecholamine excess are; hyperglycemia, fever, weight loss, panic attacks, myocardial infarction and Rynaud's phenomenon. A triad of hypertension, intermittent hematuria and symptoms upon micturation or sexual intercourse may indicate bladder extra-adrenal pheochromocytoma in almost 50% of the cases[15]. Majority of patients have paroxysmal (48%) or sustained (29-50%) hypertension. Only 2-13% may are normotensive[16,17].

Our patients we presented had both cardinal symptoms and signs of excessive catecholamine release; severe headache, palpitation, diaphoresis and labile hypertension. However the diagnosis of case 1 was delayed and inappropriate management was instituted. It is much easy to suspect a child with excessive catecholamine release than an adult or an elderly patient since they are prone to cardiovascular problems with age.

Diagnosis

The diagnosis of extra-adrenal pheochromoctomas is made both biochemically and by imaging. Biochemical diagnosis is confirmed by measurement of 24-hour urine metanephrines with sensitivity of 87-90% and specificity of 99% or greater[1819]. Plasma metanephrine levels can also be measured but has low specificity of 85% and a high sensitivity of 96%[18,20,21]. Therefore the relatively low sensitivity and high specificity of urine metanephrines leads to fewer false positives making it a screening modality of choice. Urine norepinephrine and epinephrine levels may be measured where possible. Remember that medications including; tricyclic antidepressants, decongestants, amphetamines, antipsychotic medications, reserpine, levodopa, ethanol and acetaminophen, can increase both urine and plasma catecholamine measurements and cause false positive tests[22].

We only measured the urine VMA levels which were not elevated in our patients due to lack of facilities for urine metanephrines, norepinephrines and epinephrines. It is not unusual to find normal levels of VMA in catecholamine secreting extra- adrenal pheochromocytoma or pheochromocytoma and may be misleading and this was the case in our patients[23]. Once the diagnosis of catecholamine secretion tumor is made, it must be localized.

Computer tomography (CT) has sensitivity of 98% and specificity of 92% [24, 25]. Its major limitation is that it only provides anatomic but not functional information[23].
Magnetic resonance imaging (MRI) can detect catecholamine secreting tumor in 95% of the cases and has a sensitivity of 93-100% [26]. Good in patients with iodine- based contrast allergy, children and in pregnancy. Despite this, CTS is still preferred over MRI because of lack of anatomical information.
Metaiodobenzylguanidine scan (MIBG) is a good functional test and surveys the whole body but has high false negative rate (29%) for extra-adrenal pheochromocytomas than pheochromocytomas[4].
Positron emission tomography (PET) may be used in cases of negative MIBG sca[27].
Combined PET/CT scans increases precise detection and localization, which could eventually reduce cumulative cost for additional and multiple imaging modalities[28,29].

There is no consensus on which patients diagnosed with extra-adrenal pheochromocytoma should be genetically tested for familial chromaffin-cell tumor syndromes. However, even in the absence of a suggestive family history, more than 10% of patients presenting with extra-adrenal pheochromocytoma will ultimately be found to be part of a familial syndrome[30,31,32]. Therefore, according to the guidelines of the American Society of Clinical Oncology[33] when available, patient with extra-adrenal pheochromocytoma should undergo screening for germ line mutations in *Neurofibromatosis type 1(NF1)*, *Retproto-oncogene (ret)*, *von Hippel- Lindau (VHL)*, *Succinyl dehydrogenase Subuinit complexes (B,C,D) or SDHB*,*SDHC*, and *SDHD*.

A recently published article[34] suggests that patients in whom a tumor occurs before the age of 40 or with multiple tumors may be prioritized for genetic testing. However, in our case series none of the modern localizing modalities was used except CTS. Abdominal Ultrasound Scan which is hardly described in literature for localizing catecholamine secreting tumor was used in localizing the tumors in both cases and it is still the primary localizing modality in our setting in suspected para-aortic extra-adrenal pheochromocytomas.

Management

Except in the case of widely metastatic disease, the definitive treatment of any extra-adrenal pheochromocytoma is complete surgical resection. Patients with surgically resected benign tumors have a life expectancy similar to age-matched controls[35]. The pre and intra-operative management of this tumor is unique because of the risk for hypertensive crisis and hypotensive episodes. Fortunately, most of the extra-adrenal phechromocytomas are benign and of manageable size[4,36,37].

Patients would suffer hypertensive crises due to catecholamine release during positioning of patients and surgical manipulation of the tumor. In anticipation of surgical resection, it is imperative to avoid catastrophic consequences. Therefore preoperative use of alpha adrenergic blockade for at least

2-weeks is essential in reducing surgical mortality rates and this is most often achieved with phenoxybenzamine, prazosin, or doxazosin, titrated to a systolic blood pressure of 120 mm Hg when seated and of 90 mm Hg when supine for an adult. Once alpha blockade is achieved, beta-adrenergic blockade may be initiated if the pulse rate remains > 90b/min; low doses are used initially, and gradually up titrated to a goal heart rate of 60 to 80[38].

During this time it is crucial to replete the patient's intravascular volume (which was chronically low due to inappropriate vasoconstriction) by keeping the patient on liberal salt diet[13]. In our case series, surgery was undertaken after giving alpha-adrenergic blockade for at least 2-weeks until their blood pressures returned to normal and use of moderate to high salt diet was mandatory. Both patients received beta-blockade after they became tachycardic with alpha-adrenergic blockade. This is important because starting beta-blockade prior to alpha-adrenergic blockade leads to unopposed alpha-mediated vasoconstriction and may cause "paradoxical hypertension"[13]. Some authors have advocated use of calcium channel blockers to alpha-blockade because of their role in arterial vasodilatation.

Intraoperatively, acute hypertensive crises and tachyarrhythmias may occur which may be managed with intravenous sodium nitroprusside, phentolamine and short-acting beta-blockers such as esmolol[36]. However in the patients we presented we did not encounter intraoperative acute hypertensive crises. The use of intravenous magnesium sulphate in these two patients to stabilize the heart and the good communication between the aneasthesia and the surgical team may have helped. Therefore with adequate preoperative preparation, the patient should not experience wide fluctuations in the heart rate and blood pressure.

Postoperatively, we continued hemodynamic monitoring of our patients, as the changes in vascular tone, inotropy, and glycemic control can continue to fluctuate quite rapidly in the early postoperative period. Biochemical evaluations for residual disease were performed until the acute recovery phase was successful.

Prognosis

Excision of extra-adrenal pheochromocytomas, is less well studied and likely associated with much higher morbidity and mortality. The vascularity of these tumors and their lack of encapsulation, makes these surgeries extremely challenging [37].

The largest series to date examined 25 patients with cardiac extra-adrenal pheochromocytomas undergoing surgical excision, and reported a 20% intraprocedural mortality rate, with an additional 20% of patients suffering significant complications (sepsis, myocardial infarction, and mitral valve injury) [39]. We did not have any mortality in the case series presented, probably due to the small number.

Conclusion

Extra-adrenal pheochromocytomas do exist though rare. High index of suspicion is mandatory for early diagnosis. Management for the majority of extra-adrenal pheochromocytoma is surgical. Aggressive perioperative management with alpha- and beta-adrenergic blockade and close postoperative follow-up are essential to ensure optimal outcomes. Prognosis is good though evidence of polyglandular disease should be looked for.

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