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Challenges in Management of Pheochromocytoma at a Tertiary hospital in Northern Tanzania. A 21 Years Descriptive Retrospective Study.

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Background: ***Pheochromocytomas are rare catecholamine-secreting tumors that arise from chromaffin tissue within the adrenal medulla and extra adrenal sites (paraganglioma). Due to excess secretion of catecholamines, these tumors often cause debilitating symptoms ending to death if actions are not taken. Management requires*** **competent** ***physician, surgeons and anesthesiologists.***
The main objective the study focused on pattern of presentation and treatment challenges of pheochromocytoma patients over a period of 21 years (1992- 2012)
Methods:*This was a retrospective study on patients underwent adrenelectomy at KCMC Urology Institute during the course of 21 years and histologically confirmed cases of pheochromocytoma were enrolled. A structured data collection sheet was designed with parameters of demographic data, disease presentation, investigations done, tumor localization, surgical technique and follow up, in a course of overseeing the challenges in each step of management.*
Results: ***A total of 13 patients were included in this study, median age of participants was 25 years. M:F 6:7. Majority of patients presented with clinical features related to episodic elevation of catecholamines. Localization of the tumor was done with ultrasonography, Computer Tomography scan and upon surgical exploration.12 cases were found to have right side tumor and 1 case was on the left. All cases were operated using the Chevron incision as the main surgical approach.12 patients got symptoms cured at the first 3 month visit. One died in the ward.***
Conclusion: ***Upon a study Pheochromocytoma showed to be a rare condition. Despite the challenges occurred in managing all the cases, surgery has cured in 99% of all patients operated. Radiological investigation was able to localize the tumor in 100% of the patients.***

Key words: Pheochromocytoma, challenges, management

Introduction

Pheochromocytoma is a rare tumor arising from catecholamine-producing cells in the adrenal medulla– an intra-adrenal paraganglioma (PGL), according to the World Health Organization (2004) classification, Adrenal and extra-adrenal PGLs produce significant amounts of catecholamine and give rise to the well-known clinical picture of pheochromocytoma. The parasympathetic paraganglioma (mainly in head and neck) rarely produce significant amounts of catecholamine. It is an important, often clinically occult neoplasm with devastating consequences if overlooked.[1]The first clinical description of pheochromocytoma was by F. Frankel in 1886 through a young female patient with a history of episodic attacks of headaches, palpitations and anxiety, died suddenly and postmortem examination revealed bilateral adrenal medulla tumors. In 1912 Pick coined the term pheochromocytoma when he was describing the dusky (pheo) color (Chromo) of the cut surface of the tumor when exposed to dichromate. The

first surgical excision of the pheochromocytoma was reported in 1927 by Roux who described removal of suprarenal tumor in patient with two years of episodic vertigo and nausea.[2]

Prevalence of pheochromocytoma isn't precisely known and large number of patients with PHEOs do not present with classic symptoms suggesting that majority of PHEO are not diagnosed during life[3] *Several studies have revealed familial predisposition in autosomal dominant manner*. In a large series of patients screened biochemically for suspicion of PHEO, the incidence has been reported to be as high as 1.9%, occurring equally in men and women[5]

The adrenal medulla and ganglia of the sympathetic nervous system (SNS) are derived from the embryonic neural crest. The endocrine cells of this sympathoadrenal system synthesize and secrete catecholamines and exhibit a characteristic histochemical (chromaffin) reaction when treated with oxidizing agents. During the last few years, a considerable amount of new data, concerning the genetics of PHEO/PGL, have accumulated and changed the whole approach to such patients. It has been shown that in about 25% of cases, PHEO/PGLs develop secondary to germ line mutations in any of five susceptibility genes [2,3].

A classic PHEO, a solitary tumor of the adrenal medulla, reminds us of a 'tip of an iceberg' the expression suggesting beyond a single tumor there is potentially a broader clinical picture awaiting exploration. KCMC being a referral center has been receiving complicated cases including those of pheochromocytoma. Pheochromocytoma is a life threatening tumor and if left untreated it is fatal and mortality approaches 100% due to hypertension with secondary stroke and other multi-organs failure. Since there was no collective documented study at the setting, this 21-years retrospective study overviewed the pattern of presentation and experience in managing the disease.

Patients and Methods

This study was a Descriptive Retrospective hospital based study conducted at KCMC referral hospital in institute of urology over the past 21 years. All patients who histological confirmed having pheochromocytoma were included. Data collected through registry books and medical files (1992-2012) were entered into data collection forms designed based on the specific objectives. Ethical clearance was obtained at first place.

Results

The study involved 13 patients whowere diagnosed histologically with pheochromocytoma after adrenalectomy at KCMC for a period of twenty one years. Of these, 7 were female, and they were coming from rural area. The Median age of patients was 25 years.

Clinical features

Patients with pheochromocytoma presented with different symptoms (Table 1). Eleven patients presented with persistent hypertension, two had paroxysmal hypertension.

Biochemical Evaluation and pharmacological tests

Neither biochemical tests nor pharmacological tests documented including Urine and plasma catecholamine, Vinillymandelic acid (VMA) and clonidine tests.

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Table 1. Associated Symptoms in Pheochromocytoma Patients

Symptoms Patients presented with	Number (%)
Postural hypotension	
Yes	2 (15.38%)
No	11 (84.62%)
Headache	
Yes	12 (92.31%)
No	1 (7.69%)
Anxiety	
Yes	12 (92.31%)
No	1 (7.69%)
Weight loss	
Yes	6 (46.15%)
No	7 (53.85%)
Pallor	
Yes	7 (53.85%)
No	6 (46.15%)
Flushing	
Yes	7 (53.85%)
No	6 (46.15%)
Generalized Body Malaise	
Yes	1 (7.70%)
No	12 (92.30%)
Palpitation	**13 (100%)**
Sweating	**13 (100%)**

Localization of the tumor

Localization of the tumor was done with Ultrasound, computer Tomography scan and during exploration. All were found unilateral, predominantly on the right side 11 candidates.

Preoperative preparation

All hypertensive patients were preoperatively treated with phenoxybenzamine and propranolol to control hypertension. Phenoxybenzamine was prescribed 10mg three times a day for the duration of two weeks. Experienced anaestheologist was consulted before starting stabilizing patients, during pre-operative and intraoperative care with adequate monitoring equipment.

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A minimum of two units of blood was prepared pre-operative in each patient. All patients were adequately given intravenous fluids, Ringer's lactate and normal saline for volume expansion. Phentolamine was made available to reverse hypertensive crisis.

Intraoperative events.

All 13 patients underwent open laparotomy, transperitoneal approach by Chevron abdominal incision was used in all cases. The Adrenal vein was identified and ligated first as shown in Figure 1. The tumour was gently handled in all cases. Eleven cases were found with right adrenal tumours, while 2 cases were on the left. Malignancy was reported in one patient. Neither tumour dimension nor weight measure were recorded. There were intraoperative anaesthetic challenges despite the fact that all the patients records showed stabilized blood pressure pre-operative. There were episode of hypertension and hypotension crisis which was managed with intravenous fluids like plasma expanders and blood.

Follow up

Patients were closely monitored by checking vitals sign were done in all patients including blood pressure and pulse. Twelve (12) out of 13 cases were found to be normotensive in a course of three month. Moreover all patients had their blood glucose level checked to detect hypoglycemia. One patient who intraoperative was found to have unresectable tumor died one week after operation. No patient was followed up by checking level of adrenaline and noradrenaline before and after operation. No patient had a check Ultrasound and CT scan as a control postoperatively.

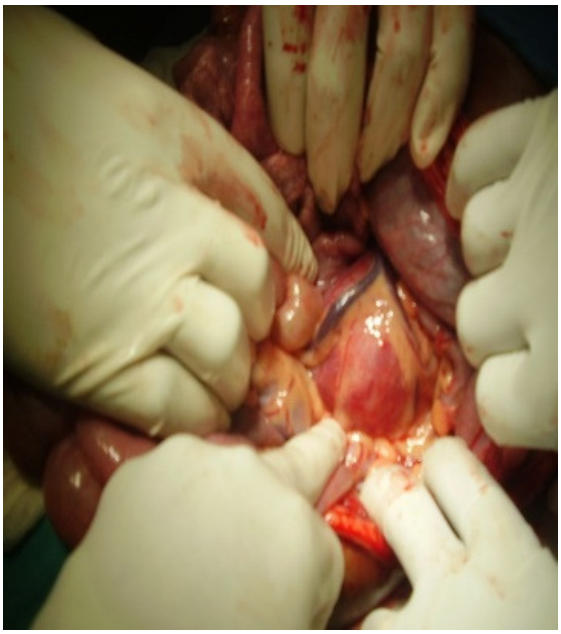

Figure 1. Adrenal vein identified first

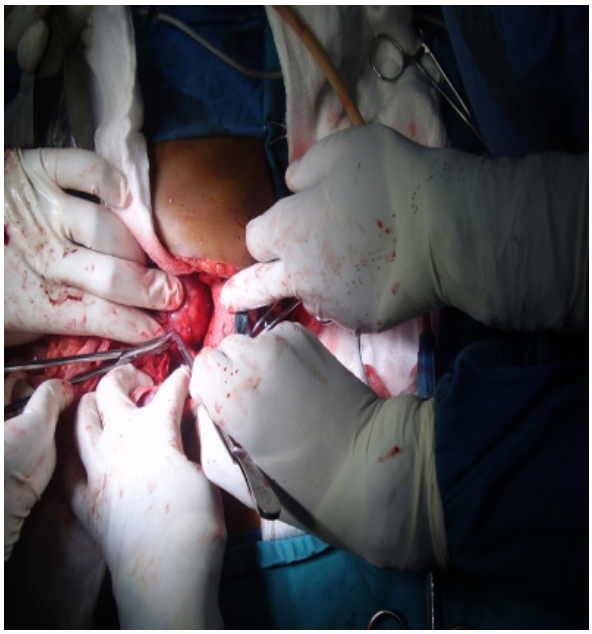

Figure 2. Adrenal vein ligated and resection continue

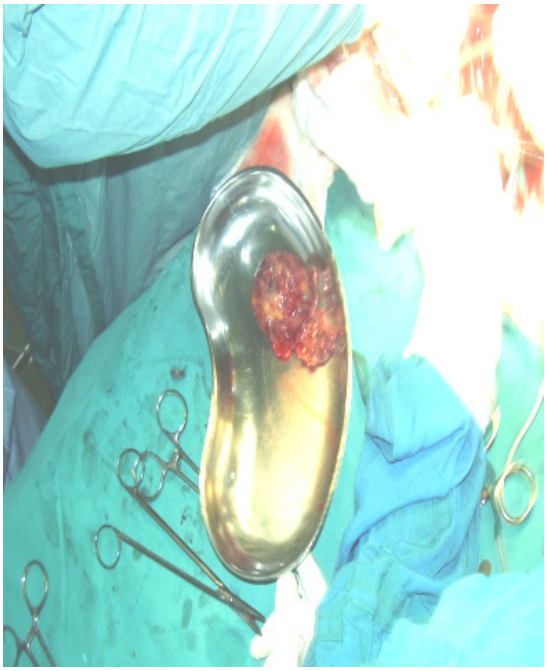

Figure 3. Sample biopsy after resection

Consent Obtained: ©Prof. A.K Mteta (2009)

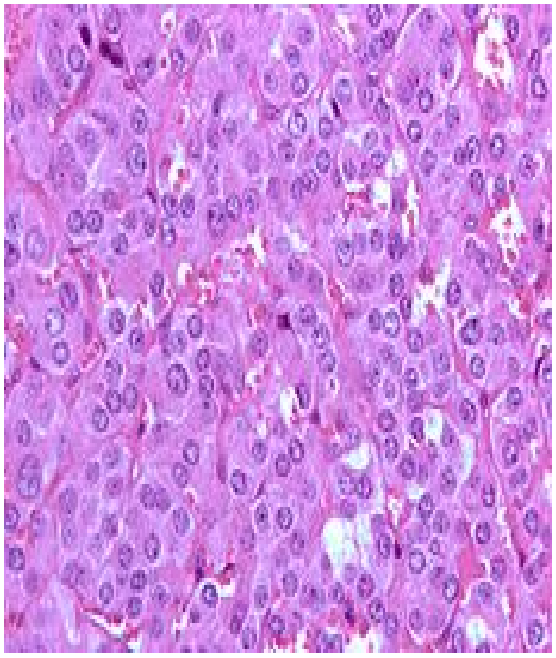

Figure 4. Histology(Zellballen)

Discussion

This study is similar to previous studies done by Berd[4]showing Pheochromocytoma is a rare condition as in 21 years duration only 13 patients were recruited. Most of the patients in this study belonged to younger age group with median age being 25 years. Pheochromocytoma was equally found in both males and females in this study similar to other studies done by Young et al [6] and a nationwide survey in 2009 by Nurse[7]. All patients were initially diagnosed clinically with signs and symptoms of hypertension, headache, palpitation and sweatiness. Data from previous studies confirm that pheochromocytoma have to be taken into account in differential diagnosis of adrenal incidentilomas and the absence of hypertension doesn't rule out the presence of Pheochromocytoma [30].

The time interval from initial clinical diagnosis to operation time was averaged to 246 days. The current study showed all patients manifested with hypertension, palpitation and sweating with other clinical features which correlate with other previous studies showing diverse manifestation reflecting the variations of hormone secretion, the pattern of release, and the individual to individual differences in catecholamine sensitivity.[6,10,17] Tumor localization relied on abdominal Ultrasound and CT scan, correlates with other studies which showed 100% sensitivity [25]

There were challenges in obtaining biochemical study in all patients; this can be a reason of delay in a diagnosis of the tumor as in similar studies has shown to establish diagnosis in more than 95% of cases [19]. There was a significant time lag from diagnosis to the introduction of pre-operative medications like phenoxybenzmine and phentolamine as per required in our

management protocol. These challenges of time lag from diagnosis to operation can be partly explained by difficulties in getting the premedication for stabilizing the blood pressure before the operation in our local set up. Also diagnosis of the tumor itself needs high clinical suspicious index, biochemical evaluation and radiological tumor localization before intervention which impose challenge in time lag before resection

Tumour localization relied on abdominal Ultrasound and CT scan, correlates with other studies which showed 100% sensitivity [25]. In this study right adrenal gland was more affected compared to the left adrenal gland, in contrast with a study done by Krishnappa et al [12]. which showed 5 left adrenal gland out of total 7 cases were affected

Pre-operatively all cases received phenoxybenzamine in a minimum of four weeks in a dose range 20-40mg and propranolol to stabilize hypertension and arrhythmias respectively as in previous studies showed. Arterial line placement and preoperative correction of intravascular volume was done [17]. In our study all patients were evaluated adequately with anaesthesiologist and hypertension stabilized with α blocker medications before given β blockers and intravenous fluids.

Intra-operatively anesthesiologists took special consideration to control blood pressure by giving phentolamine and propranolol and proper monitoring of all vitals.

The operative management of patients with pheochromocytoma may be complicated by large and potentially lethal swings in blood pressure with high peaks during tumor handling and severe hypotension immediately following removal of the tumor [32]. Hypotensive episodes occurred intraoperative were managed by volume replacement with crystalloids and blood.

There was no intra-operative mortality in all patients. 12 patients out of thirteen stabilized blood pressure 1 month post-operative during the follow up. This is similar to other literatures which concluded that there is little mortality if the patient is prepared well and blood pressure stabilized before operation.

Conclusion

Pheochromocytoma is a rare condition, challenging in management but surgically cured as shown this study. The clinical features of pheochromocytoma vary between hypertension, headache and sweating manifest in all cases in current study. Despite the challenges in diagnosis, ultrasound and CT scan play a big role in tumor localization. Biochemical studies should be initiated in diagnosis of pheochromocytoma which will help to in early diagnosis of a condition.

Our patients presented late in our department as they have to pass in different department like internal medicine department before they came in urology department which can be one factor to explain delay of operation from date of diagnosis. Moreover preoperative medications like phenoxybenzamine intraoperative medications e.g. phentolamine had to be purchased by patients as they were not locally available and this delayed the operation.

There were challenges in histopathological description of the tumour as in all histology results none showed if it is malignant or benign.

Surgery is the main stay of treating pheochromocytoma despite the intraoperative challenges.

Recommendations

- We need multicenter studies to evaluate magnitude of the problem and long follow up of the patients.

- Phenoxybenzamine is effective in the preoperative management of Pheochromocytoma. Drugs like phenoxybenzamine and phenntolamine should make readily available to reduce the duration from diagnosis to operative time.
- In this study we have seen the importance of CT scan and how have it contributed in localization of the tumor. This diagnostic instrument should be available all the time.
- There is a need to do adrenal autopsy for all the cases that dies with essential hypertension and its complications to rule out pheochromocytoma enabling us to have a clear picture of disease.
- There is a need to do a study on follow up of all patients diagnosed with pheochromocytoma and operated on their progress including recurrence and quality of life afterwards.

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