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Case Report

Biochemically silent normotensive colossal pheochromocytoma

Saravana Kumar I.*, Ketan D. Mehta

Department of General Surgery, Shri M. P. Shah Medial College, Jamnagar, Gujarat, India

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***Correspondence:**
Dr. Saravana Kumar I.,
E-mail: Sarsandivis12@gmail.com

ABSTRACT

A case presentation about rare giant pheochromocytoma of about a 50 year old female patient came to our out-patient department of general surgery with epigastric and right flank discomfort for past 1 day, abdominal distension and constipation for past 6 months. Patient's blood pressure was normal without any postural variations and with no features of androgenic excess. All routine investigations were normal. Biochemical profile of urinary [VMA, metanephrine and normetanephrine], serum [cortisol, metanephrine, normetanephrine], serum aldosterone and plasma renin activity are measured normal. Contrast enhanced CT abdomen done suggestive of large well defined heterogeneously enhancing soft tissue lesion of size 21×22×28 cm noted involving abdominal cavity more on right side arising from right lumbar region was identified. Patient underwent exploratory laparotomy and identified that mass was arising from right adrenal gland and right kidney which was difficult to be dissected from the mass, for which right nephrectomy was also done along with mass removal of size 28×28×20 cm and weight of 4200 gm. Postoperative period was uneventful. Histopathological examination showed gross feature of single large encapsulated globular structure with right kidney attached to it. Mass was encapsulated with total size of 24×25×14 cm, greyish in colour and soft to firm in consistency. On cut section focal areas of greyish yellow friable tissue with few small cystic areas, large hemorrhagic area and focal greyish white areas was seen. Microscopic feature of these tumor cells was arranged in well defined nests (zellballen) bound by highly vascularized stroma. Cells were polygonal shaped with finely granular amphophilic cytoplasam, round to oval nuclei with salt and pepper chromatin and at places prominent nucleoli were seen. Special staining with PAS done and it was negative.

Keywords: Giant pheochromocytoma, Paraganglinoma, Normotensive

INTRODUCTION

Pheochromocytoma is a rare functioning tumor of adrenal medulla and extramedullary sympathetic ganglia and derived from catecholamine producing chromaffin cells.[1] It constitute 4% to 8% of incidentally detected adrenal masses.[2] It is also known as the "ten percent tumor "as ten percent of tumors are inherited, ten percent are extraadrenal, ten percent are malignant, ten percent are bilateral and tenpercent occur in children.[3] Most cases are sporadic, but they may be associated with multiple endocrine neoplasia type 2 (MEN2), vonHippel-Lindau syndrome (VHL), and less commonly neurofibromatosis type 1 (NF-1).[4,5]

Although frequently associated with hypertension, 5-55% of patients will be normotensive. Due to this, they may be incidentally discovered or go undiagnosed without the paroxysmal nature of the hypertension or the presence of orthostatic hypotension on standing. Lower concentrations of catecholamines may be seen more in normotensive patients than in those who are hypertensive. While it makes sense that the extent of symptoms is related to the concentration of catecholamines produced, this does not necessarily correspond to size of the tumour on imaging.[6] Despite major advances in the biological tools to diagnose these tumors a significant number of pheochromocytomas are undiagnosed and found incidentally during radiological abdominal investigations.[7-9]

The approach to the workup of a suspected pheochromocytoma includes biochemical studies as well as imaging. Plasma free metanephrine testing may be performed first. Due to the low specificity of this test, a positive result should prompt confirmation with measurement of 24-hour urinary catecholamines and their metabolites.[10] For imaging studies, MRI is preferred for localization because contrast media used in CT scan can provoke paraxosyms. 123I MIBG (Meta iodo benzyl guanidine) scan will identify ninety percent of primary tumors and is essential for the detection of multiple extra adrenal tumors and metastasis and fluorodeoxyglucose positron-emission tomography.[3]

Laparoscopic resection is nowadays a routine treatment of pheochromocytoma. If tumor is larger than 8-10 cm or radiological signs of malignancy are detected, an open approach is considered.[3]

CASE REPORT

A 50 year old female patient came to our out patient department of general surgery with epigastric and right flank discomfort for past 1 day, abdominal distension and constipation for past 6 months. On per abdomen examination, a huge mass involving the whole of the abdomen having solid consistency, non-tender and non-mobile. Past history and family history were non contributory. General examination was normal. Patient's blood pressure was normal without any postural variations with no features of androgenic excess, Cushing's syndrome or neurocutaneous markers.

Routine blood investigations and chest X-ray were within normal range. Pheochromocytoma was clinically suspected, therefore 24 hourly urinary VMA, metanephrine, normetanephrine levels were performed which were normal, plasma free metanephrines 0.30 nmol/l (normal, <0.50 nmol/l) and plasma free normetanephrines 0.40 nmol/l (normal, <0.90 nmol/l). Overnight 1-mg dexamethasone suppression test was appropriate, with suppressed morning cortisol level of 1.2 µg/dl. Serum aldosterone was 18 ng/dL, and plasma renin activity was 15.2 ng/ml/hour (ratio<20). So biochemical profile was normal. Patient underwent sonography abdomen which was suggestive of roughly more than 50×40 cm size giant complex solid cystic mass involving the whole of the abdomen with origin right renal or adrenal origin. Then CECT performed which was suggestive of large well defined heterogeneously enhancing soft tissue lesion of size 21×22×28 cm noted involving abdominal cavity more on right side arising from right lumber region cranio-caudally it extends from upper border of D9 vertebrae to upper border of sacrum it displaces right kidney and right ureter inferomedially which lies in left iliac fossa and shows normal parenchymal enhancement and excretion.

Patient was posted for exploratory laparotomy then a midline vertical incision made (Figure 1) and identified that mass was arising from right adrenal gland and right kidney which was difficult to be dissected from the mass (Figure 2), so right nephrectomy was also done along with mass removal of size 28×28×20 cm and weighing 4200 gm being excised (Figure 3).

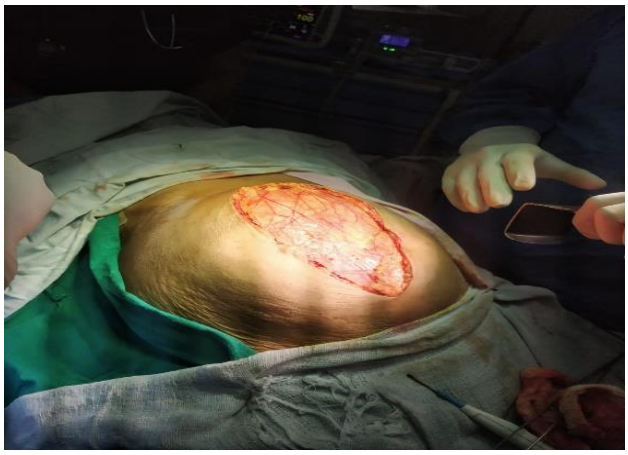

Figure 1: Midline incision of exploratory laparotomy.

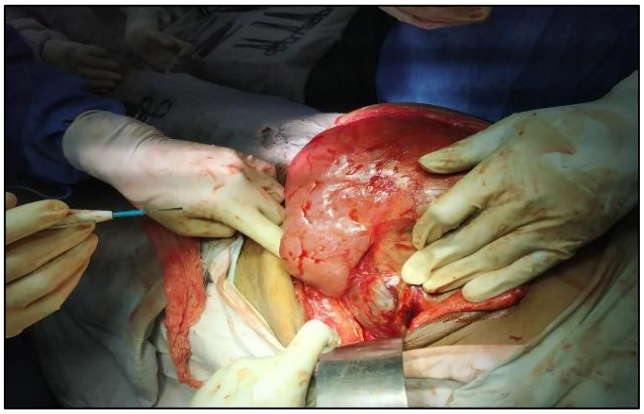

Figure 2: Intact right kidney with right adrenal mass (inseparable).

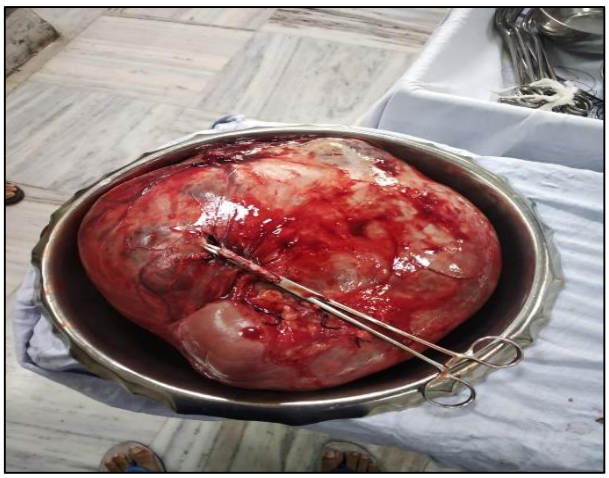

Figure 3: Excised mass with right kidney of size 28×28×20 cm with clamped applied over renal artery, renal vein, renal pelvis all together.

Post operative period was uneventful with sips orally on day 3, soft diet on day 5, all suture removal done on day 14 (Figure 5).

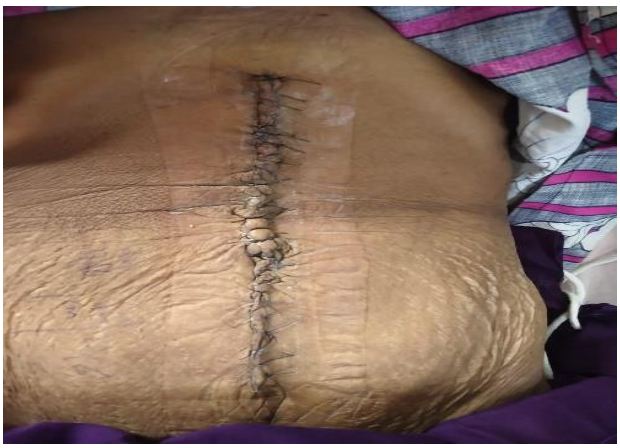

Figure 5: Post operative wound of patient.

Patient's histopathological report came, suggestive of pheochromocytoma.

Gross features

Single large encapsulated globular structure with right kidney attached to it. Mass was encapsulated total of size 24×25×14 cm greyish in colour and soft to firm in consistency. On cut section focal areas of greyish yellow friable tissue with few small cystic areas, large hemorrhagic area and focal greyish white areas were seen (Figure 6). Right kidney of total size (9×7×3 cm) greyish white in colour and firm in consistency.

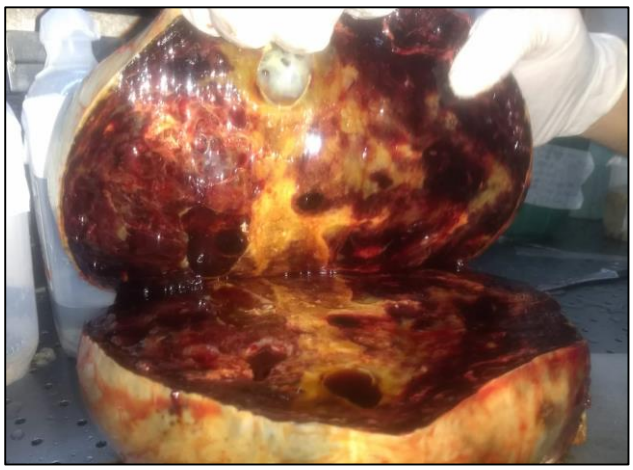

Figure 6: Gross appearance of excised mass.

Microscopic features

It shows distinct fibrous capsule beneath with layers of adrenal glands namely zona glomerulosa, zona fasiculata, zona reticularis were appreciated (Figure 7). These tumor cells were arranged in well-defined nests (zellballen) bound by highly vascularized stroma. Cells were polygonal shaped with finely granular amphophilic cytoplasam, round to oval nuclei with salt and pepper chromatin and at places prominent nucleoli were seen. (Figure 8). Special staining with PAS was done and it was negative.

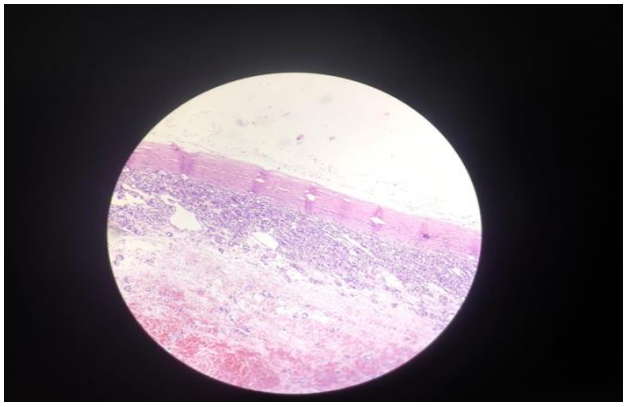

Figure 7: Microscopic image with layers of adrenal gland zona glomerulosa, zona fasiculata, zona reticularis.

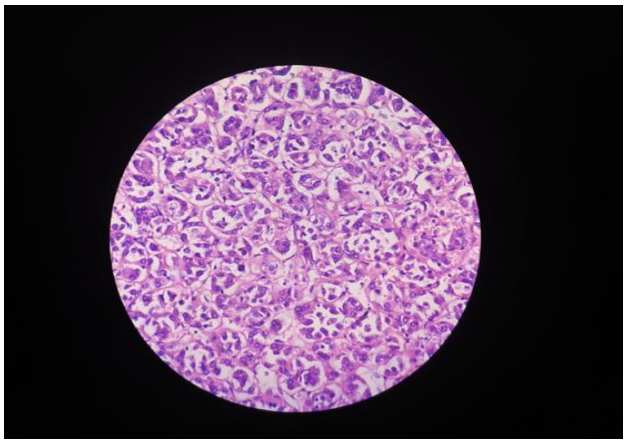

Figure 8: Microscopic image showing "Zellballen pattern".

DISSCUSION

Pheochromocytoma is tumors of the adrenal medulla and of chromaffin tissues in the other parts of body (paragangliomas) They secrete epinephrine or nor epinephrine, resulting in sustained or episodic hypertension and other symptoms of catecholamine excess.[11] Most Pheochromocytomas occur sporadically, but they may be associated with various familial syndromes such as multiple endocrine neoplasia (MEN) 2A (medullary thyroid carcinoma, Pheochromocytoma, and hyperparathyroidism), MEN 2B (medullary thyroid carcinoma, pheochromocytoma, mucosal neuromas, marfanoid habitus, and ganglioneuromatosis), von Recklinghausen disease, von Hippel-Lindau disease.[12]

Several authors have described the occurrence of normotensive pheochromocytoma; Agarwal et al presented their experience on normotensive pheochromocytoma and justified the use of preoperative α-blockade in this condition as undertaken for hypertensive pheochromocytoma.[13] Shao et al in 2011 described preoperative α-blockade has no advantage in sustaining hemodynamic stability in patients with normotensive pheochromocytoma and can augment the use of vasopressor drugs and colloid infusion.[14]

The approach to the workup of a suspected pheochromocytoma includes biochemical studies as well as imaging. Plasma free metanephrine testing may be performed first. Due to the low specificity of this test, a positive result should prompt confirmation with measurement of 24-hour urinary catecholamines and their metabolites.[10] Imaging studies include CT or MRI, with or without additional nuclear studies such as iodine-123 MIBG scintigraphy and fluorodeoxyglucose positron-emission tomography.[15,16] The amount and pattern of the catecholamines secreted usually account for hemodynamic features of patients with pheochromocytomas.[17,18] The pattern of catecholamines secretions from the tumor can be continuous, episodic, or both.[19] There are some evidences that low amounts of circulating catecholamines and intermittent release were associated with weak clinical presentations.[4] Blood levels of catecholamines of "silence" pheochromocytomas were lower than symptomatic patients with pheochromocytomas.[20] This study also indicated that urinary free catecholamines (Epinephrine and norepinephrine) were decreased 3-to 10-fold in patients with normotensive pheochromocytoma than those with hypertensive pheochromocytoma. Further, each type of catecholamines has varied impact on blood pressure. Patients with tumors that produce high concentrations of norepinephrine are likely to incur sustained hypertension, whereas patients with significantly elevated levels of epinephrine often have paroxysmal hypertension and orthostatic hypertension, and patients with Dopamine secreting tumors are most often normotensive.[21] This hemodynamic change showed that there was consistent with pathophysiological basis between activity of catecholamines secretions and clinical manifestations.[22] In this study tumor weight linearly related to 24 h urinary noerpinephrine in hypertensive pheochromocytoma group, while the relation has not been found in normotensive group. The amount of catecholamines and phenotypic presentations in Normotensive group may be associated with the pathological phenotype variability and form through special biochemical phenotype *in vivo*.[23-26] Ultimately, this study showed that the positive percentage of E-type of catecholamine in hypertensive group was higher than those of the normotensive, while the positive percentage of norepinephrine type or no function of catecholamine in hypertensive group was lower than those of the normotensive, which were determined by 24 h urinary catecholamines metabolites.[27] There was literature reported that specific molecular defects in the chromaffin cellular machinery account for the peculiar biochemical and clinical phenotype of normotensive's.[28]

On unenhanced CT, pheochromocytomas may be homogeneous or heterogeneous, solid or cystic complex masses or may show bleeding, cystic degeneration, necrosis and calcification.[29] Almost all pheochromocytomas have attenuation values of greater than 10 HU; rarely do they contain sufficient intracellular fat to have an attenuation of less than 10 HU.[30] On enhanced CT, pheochromocytomas may show homogeneous or variable enhancement and most cases show avid enhancement of the solid components.[29] However some cases show heterogeneous or show regions of no enhancement due to cystic changes.[31] There is no obvious difference between HPs and NPs by reviewing CT pictures.

Surgical excision is the only chance for cure. Even in patients with metastatic disease, tumor debulking can be considered to reduce the tumor burden and to control the catecholamine excess.[32] In my case study tumor was excised surgically.

Basso L and colleagues reported the biggest pheochromocytoma of size 29×21×12 cm weighing about 4050 grams with no sign and symptoms of catecholamine excess.[33] There are few published cases of pheochromocytoma larger than 20 cm, one of them was reported by Arcos et al about malignant pheochromocytoma with largest dimension more than 20 cm. In my case study the size of the tumour was 28×28×20 cm and weighing 4200 gm.[34] A literature search yielded a case report by Maharaj et al which provided a summary of all giant pheochromocytomas (defined as tumors >10 cm) reported in the literature.[35] The largest tumor reported by Maharaj et al was 45×20 cm originally described by Grissom et al in 1979.[36] Thirty-seven cases of giant pheochromocytomas were cited.

Approximately ten percent of pheochromocytomas are malignant. This rate is high in extra adrenal tumors (paragangliomas). The diagnosis of malignancy implies metastasis of chromaffin tissue, most commonly to bone, lymph nodes and liver.[3,37,38]

Macroscopic features

Phaeochromocytoma are soft, encapsulated tumours with a yellow/brown to red cut surface and may weigh from just a few grams to up to 4 kg. Larger tumours can show areas of necrosis, cystic degeneration or haemorrhage. They usually have a thin rim of compressed adrenal cortex peripherally. If potassium dichromate is added to fresh tumour, it will turn dark brown (chromaffin reaction). Microscopically, the tumour cells have round to oval nuclei with a prominent nucleolus and may contain cytoplasmic inclusions. The cells have a finely

granular basophilic or amphophilic cytoplasm and are usually arranged in nests (Zellballen pattern) surrounded by a rich vascular network Marked nuclear pleomorphism and hyperchromasia can be seen but similar to capsular and vascular invasion, this in itself is not a reliable indicator of malignancy. Mitoses are rarely found. Occasionally, the tumour cells may have an oncocytic appearance due to the presence of large numbers of mitochondria. Other features include ganglion-like cells, dystrophic calcification and melanin pigment and the presence of amyloid.[39,40] The nests are outlined by sustentacular cells, which provide structural support and are not visible with routine staining techniques, but can be highlighted with S-100 immunocytochemistry. paraganglinomas can be associated with other tumours of the adrenal medulla, such as ganglioneuroma, ganglioneuroblastoma or neuroblastoma, and with other tumourssuch as adrenal cortical adenoma, spindle cell sarcoma or neuroendocrine carcinoma.[41,42] Hyperplasia of the adjacent adrenal medulla can be an indication of MEN-2 syndromes, but it is difficult to identify and genetic screening is more accurate.[43]

CONCLUSION

In conclusion pheochromocytoma is a rare but clinically important disorder because of its high morbidity and mortality. Surgical removal is the mainstay of treatment. Even in case of normal biochemical studies, the tumor should be removed.

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