

Case Series

Diagnostic and therapeutic challenges in the management of silent and functional giant pheochromocytoma

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ABSTRACT

Giant pheochromocytoma is a rare retroperitoneal tumor that is "clinically and biochemically quiet" most of the time, posing diagnostic and treatment hurdles in ordinary surgical practice. This case study includes four participants. The average age of the patients was 56.5 years. Two patients exhibited symptoms and biochemical diagnostic characteristics, but the other two were clinically and biochemically silent. Preoperative imaging revealed the diagnosis in two individuals. In two patients with an initial diagnosis, all patients underwent laparotomy after preoperative preparation and stabilization. The diagnosis of giant pheochromocytoma was confirmed histopathologically in all four individuals with a PASS score of less than 3. All patients were disease-free and were being followed on a routine basis. Even though it is uncommon, "clinically and biochemically silent" Giant pheochromocytoma should be considered as a differential diagnosis of retroperitoneal tumor, where preoperative diagnosis by imaging and biopsy, alongside patient preparation and stabilization, reduces adverse intraoperative and postoperative events.

Keywords: Endocrine, Surgery, Giant pheochromocytoma, Silent pheochromocytoma

INTRODUCTION

Pheochromocytomas are tumors arising from the adrenal medulla. Classical presentations seen in these tumors are headache, sweating, palpitations and hypertension. Around 20%-30% of adrenal pheochromocytomas are asymptomatic. Pheochromocytomas greater than or equal to 7 cm are by definition considered Giant Pheochromocytomas.¹ Such giant pheochromocytomas were occasionally reported to be non-functional which is a plausible explanation for their clinical and biochemical silence. Owing to their large size, factors like intra-tumoral hemorrhage, liquefactive necrosis, interstitial tissue without bioactivity, paucity of the release of the catecholamines due to encapsulation by the connective tissue may lead to the inability to secrete biochemically active components. Such clinically and biochemically

silent giant pheochromocytomas can often be mistaken for other tumors like retroperitoneal sarcomas, lymphomas, pancreatic malignancies arising from retroperitoneum, etc.² The multi-modality approach is recommended for optimum management of "clinically and biochemically" silent giant pheochromocytomas. Surgical resection is the only modality to achieve a complete cure. Management of giant pheochromocytomas is associated with multiple challenges that include preoperative diagnosis, optimization prior to surgery, intraoperative surgical difficulties related to exposure, tumor handling, need for multi-organ resections and medical challenges like change in hemodynamics and risk of cardiovascular events. Adrenal tumors with a size >6 cm harbour a greater chance of being malignant. Aggressive tumors can be predicted by PASS (pheochromocytoma of

adrenal origin scaled score) score which is suggestive but not definitive to diagnose malignant pheochromocytomas.³ Given the rarity of such tumors, there are only case reports published in English literature to date. Here, we present case series of four patients with “giant pheochromocytoma” masquerading as retroperitoneal tumor along with the diagnostic and therapeutic challenges we have faced in their management.

CASE SERIES

The study included a total of four patients. The mean age was 56.5 years (72-43). Two of the four patients exhibited specific symptoms, while the other two were assessed for non-specific symptoms. Preoperative biochemical analysis, imaging studies such as ultrasonography (USG), contrast-enhanced computerized tomography (CECT) of the abdomen, magnetic resonance imaging (MRI), 18F-DOTA Positron emission tomography (PET), and 131I-or123I-labelled

metaiodobenzylguanidine (MIBG), and percutaneous cytology were performed on the patients (Figure 1 and 2 A and B). Two individuals were clinically and biochemically quiet, whereas the other two exhibited high catecholamine levels and symptoms. Following preoperative examination and stabilization, all patients underwent laparotomy. One week to before surgery, patients with a clinical diagnosis of pheochromocytoma were started on the alpha-blockers tab. prazosin 2.5 mg BD, followed by beta-blockers/calcium channel blockers and daily hydration with 5-6 litre/day salt-rich fluid orally. The goal was to achieve a systolic blood pressure of 130 mm Hg when lying down, with orthostatic hypotension predicted. Episodes of hypertensive crises were treated intraoperatively with nitroglycerine and nitroprusside infusion, and post-resection hypotension was treated with norepinephrine and vasopressor support. All patients were followed up on until the end of their hospital stay, including outpatient visits to the surgical department. Tables 1 and 2 present data on patient characteristics.

Table 1: Patient characteristics and evaluation parameters.

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Age (Years)	72	56	43	55
Symptoms	Hypertension per abdomen lump	Dull aching pain abdomen	Lump abdomen	Hypertensive tremors palpitations
24 hours, VMA (2.20-7.50) mg/24 hours	1.2	2.69	-	45.15
24 hours, urine metanephrine (36-190) µg/24 hours	65	40.66	-	>10000
24 hours, urine nor-metanephrine (35-482) µg/24 hours	2350	56.4	-	5473.55
Adrenaline (0 to 140 pg/mL)	-	85	-	-
Noradrenaline (70 to 1700 pg/mL)	-	136	-	-
CECT abdomen	14×10×11 cm Left adrenal gland not visualized Separately para-aortic lymphadenopathy	7.5×6.5×3.2 cm Precaval region retroperitoneum inferior to D3/D4 segment	21.3×18.7×23 Occupied whole of left side of abdomen Ill-defined fat planes with pancreas, spleen and splenic flexure of colon (Figure 3 A)	9×6 cm Right suprarenal retrohepatic region
MIBG	Increased tracer uptake with no mets	Not performed	Not performed	Not performed
Dotate PET CT	Not performed	Not performed	No tracer uptake	No tracer uptake
Pre-operative biopsy	Not performed	USG guided pheochromocytoma	--	--
Pre-operative stabilization	Hydration 4-5l/day tab. prazosin 2.5 mg BD tab. amlodipine 5 mg OD	Pre-operative fluid therapy	---	Hydration 5-6 l/day Tab. prazosin 10 mg BD followed by Tab metoprolol 25 mg BD

Table 2: Intra-operative and post-operative events.

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Type of procedure	Laparotomy	Laparotomy	Laparotomy	Laparotomy
Incision	Left L shaped	Midline	Midline	Right sub costal
Procedure	En bloc resection of tumor (Figure 1 A and B)	Excision (Figure 1 C and D)	En bloc resection of tumor + left nephrectomy + left hemicolectomy and end colostomy (Figure 3 B)	Right adrenalectomy
Intra operative events	Uneventful	Hypertension	Hypertension	Hypertension
Post-operative complications	Uneventful	Uneventful	Hematuria, chylous leak	uneventful
Post-operative stay	5 days	4 days	11 days	5 days
Pathology	Pheochromocytoma	Pheochromocytoma (extra adrenal gonadal ring)	Pheochromocytoma (Malignant)	pheochromocytoma
Weight	735 gm	320 gm	5600 gm	140 gm
PASS score	2	2	3	2
Follow up	18 Months	10 months	3 months	6 months
Recurrence	Nil	Nil	Nil	Nil
Specific features	Giant symptomatic	Giant clinically and biochemically silent differential diagnosis was cystic neoplasm of pancreas	Giant clinically and biochemically silent Differential diagnosis was large retroperitoneal sarcoma, large pancreatic neoplasm malignancy on post op pathology, need adjuvant therapy	Giant symptomatic

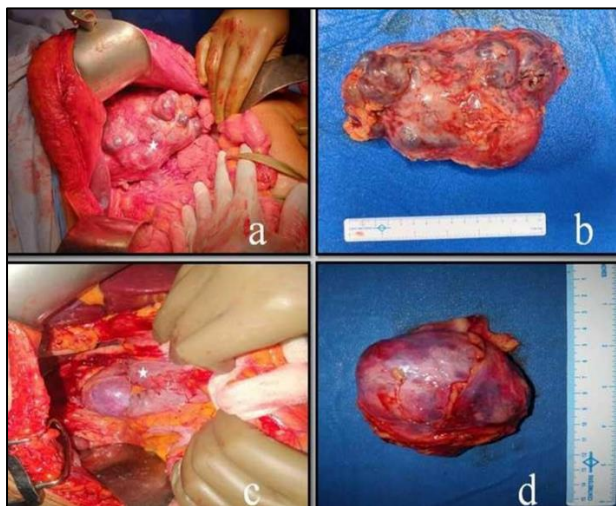


Figure 1 (A-D): Intraoperative image of multicystic giant pheochromocytoma arising from left adrenal gland, gross specimen showing multi cystic giant pheochromocytoma of 15×15 cm, intraoperative image of multicystic giant pheochromocytoma from right adrenal gland and gross specimen showing multi cystic giant pheochromocytoma of 9×6 cm.

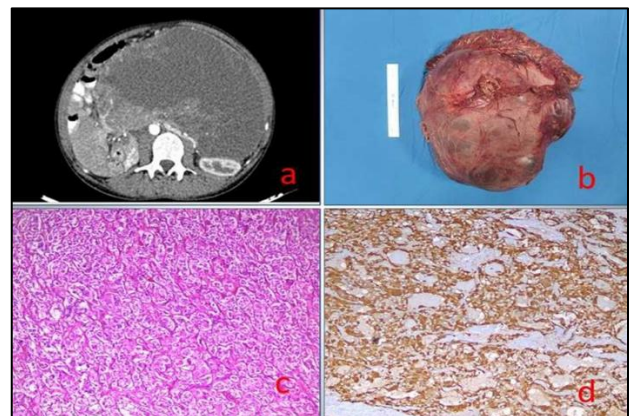


Figure 2 (A-D): CT image showing a large 21.3×18.7×23 cm heterogenous tumor arising from left side retroperitoneum with ill-defined fat planes with surrounding organs, gross specimen-multicystic giant pheochromocytoma tumor of 20×20 cm size. A cellular tumor arranged in nests, separated by thin vascular septae. The cells show abundant granular basophilic cytoplasm (Hematoxylin and Eosin, ×100). The tumor cells show diffuse and strong chromogranin expression (IHC, x100).

Histopathology revealed that all patients had characteristic pheochromocytoma features. In all instances, the PASS (pheochromocytoma of the adrenal gland scaled score) was less than 3. Tumor cells displayed synaptophysin and chromogranin in all cases, and S-100 identified sustentacular cells. Except in case 2, when it was 4-5%, the Ki-67 proliferation index was less than 3% in all cases (Figure 2 C and D).

DISCUSSION

Pheochromocytomas are neuroendocrine tumors that arise from the adrenal medulla or sympathetic ganglia and have an annual incidence of 2 to 8 per million persons. "Clinically quiet pheochromocytoma" refers to tumors that lack the usual triad of symptoms, while "Biochemically silent pheochromocytoma" refers to tumors that lack elevated catecholamine levels in blood and urine.

Giant pheochromocytomas are rare tumors, and clinically and functionally silent giant tumors are even more uncommon, with just a few case reports available. There have been 36 cases of giant pheochromocytoma documented in the literature so far. This is the first case series of four patients with giant pheochromocytomas, two of whom were clinically and biochemically quiet.

Cystic PCC may contain relatively few functional cells, making it difficult to detect such cases before surgery. Retroperitoneal sarcoma, cystic pancreatic neoplasm, lymphoma, and adrenal incidentaloma are typical differential diagnoses. Failure to detect them before resection may result in intraoperative hypertension, postoperative hypotension, and an increased risk of cardiac events such as arrhythmia [4].

Biochemical measurements of 24-hour urine fractionated metanephrines and catecholamines, as well as plasma fractionated metanephrines after 30 minutes of supine rest, can be used to detect "giant clinically silent pheochromocytoma." The sensitivity of CECT/CEMRI imaging modalities ranges from 98% to 100%, with a specificity of 70%. The availability and cost of CT and MRI affect the choice.⁵

Pheochromocytoma imaging characteristics included increased attenuation on nonenhanced CT (>10-20 Hounsfield units), increased mass vascularity, high signal intensity on T2 weighted images, delay in contrast medium washout (10 minutes after contrast administration, less than 50%), cystic, haemorrhagic, and necrotic changes.

Functional imaging, such as a metaiodobenzylguanidine (MIBG) scan, should be conducted in patients suspected of having an indefinite diagnosis, multifocal or metastatic illness, as it assists in sufficient preoperative preparation in such uncommon circumstances prior to surgical excision. MIBG is highly

specific for pheochromocytoma, however, its sensitivity ranges from 77 to 90%.⁶ PET-CT/FDG 18F-DOTA PET scans are more sensitive than MIBG scans, although they are only available in a few centres. FNAC may be used to confirm the diagnosis and to prepare the patient for surgery in order to avoid intraoperative problems and decrease morbidity and mortality. The use of FNAC for pheochromocytoma is typically avoided due to the possibility of inducing a hypertensive crisis, which is a rare incidence recorded in the literature. The presence of a high index of suspicion in conjunction with anatomic location and a distinctive cytological appearance may aid in the diagnosis of clinically silent pheochromocytoma.⁷

PASS scoring is used histologically to diagnose high-risk lesions for cancer. Lesions with a PASS score of less than 4 are considered low risk, while those with a score of more than 4 are considered high risk. Pathological features such as vascular invasion, capsular invasion, extension into periadrenal adipose tissue, the presence of focal or confluent necrosis, high cellularity, tumor cell spindling, cellular monotony, >3 mitoses per high-power field, atypical mitotic figures, profound nuclear pleomorphism, and increased tumor cell hyper-chromasia are all taken into account by this scoring system.^{8,9}

However, it is presently thought that all instances of pheochromocytoma, regardless of PASS score, have malignant potential. The only curative option for these massive tumors is surgical resection. Large adrenal tumors that are possibly malignant carcinomas with infiltration into surrounding organs necessitate open surgery. Pre and post-operative blood pressure management with catecholamine blockers and intravenous fluids are thought important for straightforward pheochromocytoma excision. In the presence of giant lesions, open en bloc tumor excision is safer than laparoscopic resection. Optimal exposure with a generous incision allows for adequate visibility of lesions and minimum lesional changes. Minimal handling of lesions, early separation of venous drainage, minimizing capsule breaching, and strong cohesion with the anaesthesia team all contribute to minimising adverse occurrences intraoperatively. Thorough blood pressure monitoring in the postoperative period is also recommended to minimize complications caused by hypotension episodes.^{2,4,8}

CONCLUSION

"Clinical and biochemically," a silent large pheochromocytoma is an exceptionally unusual tumor; the conventional triad of symptoms may not be present owing to cystic degeneration of the tumor, which results in the minimal functioning of sympathetic cells with catecholamine release. In patients presenting with left-sided retroperitoneal tumor characteristics, a high index of suspicion for a giant pheochromocytoma should be maintained. Imaging and biochemical tests should be

undertaken to avoid intraoperative and postoperative problems.

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