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Case Report

A case report on asymptomatic and biochemically silent pheochromocytoma in adrenal incidentaloma

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ABSTRACT

Pheochromocytoma are rare tumours originating from the chromaffin tissue. The clinical manifestations are variable and are not specific as pheochromocytoma and often imitate other diseases. The diagnosis is established by measurement of catecholamines and their metabolites in urine or plasma and by radiographic studies for localisation. Surgical removal of the tumour is the preferred treatment. 45 years old female presented with adrenal incidentaloma of about 6.1×6.2×5.4 cm well defined heterogenous lesion with internal cystic areas seen in right adrenal region abutting upper pole of right kidney. Biochemical investigations for adrenal hormones including plasma aldosterones, cortisols, plasma metanephrines, 24 hrs urinary metanephrines and VMA were found to be normal. Proceeded with adrenelectomy and histopathology of the specimen revealed pheochromocytoma as diagnosis. Pheochromocytoma leads to high mortality and morbidity rates if untreated. Fractionised metanephrines and catecholamines in a 24 hrs urine analysis is the preferred biochemical test. In a biochemically silent pheochromocytoma imaging modalities are used to identify and locate the tumour. Adequete alpha and beta blockade should be ensured before tumour removal. Surgery is recommenced irrespective of size and normal biochemical study to prevent complications.

Keywords: Pheochromocytoma, Adrenal incidentaloma, Urinary metanephrines and catecholamines, Adrenelectomy

INTRODUCTION

Pheochromocytomas are catecholamine producing neuroendocrine tumors arising from the adrenal medulla. Their prevalence is 0.1 to 0.6 percent and 80 to 85 percent of them arise from adrenal medulla. Similar, tumors that develop outside adrenal glands along the sympathetic or parasympathetic chain are referred to as paragangliomas.

In general, tumors of the adrenal medulla and sympathetic chain are secretory. They produce the catecholamines epinephrine, norepinephrine, dopamine or their metabolites metanephrine, normetanephrine, or methoxytyramine.

Typical symptoms associated with secretory pheochromocytomas include sustained or episodic hypertension, headache, palpitations, sweating, and pallor. These symptoms can happen spontaneously or triggered in certain situations such as induction of anesthesia, tumor manipulation, micturition, and exposure to specific medications, such as tricyclic antidepressants, tyramine, metoclopramide, steroids, and glucagon. Biochemical testing with plasma free metanephrines or 24-hour urinary fractionated metanephrines is done.[1] If incidentally found to have an adrenal mass, they should also be screened for plasma or urinary metanephrines.

Mortality is high in patients with secretory pheochromocytoma undergoing surgery without pre-operative medical therapy. To reduce mortality associated with removal of these tumors, all secreting Pheochromocytomas should be treated with alpha-blockade (with or without beta- or calcium- channel blockade) for at least 2 weeks or until stable, prior to undergoing a planned surgical procedure. However, if biochemical testing is negative, pre-operative medical preparation is not performed.

CASE REPORT

45 years old female patient presented with adrenal incidentaloma presented on CT scan. She did not have any complaints of episodic headaches, palpitations, sweating, chest pain, or hypertension. There was no history of weight gain, excess hair growth on the body, acne, proximal muscle weakness, or menstrual irregularity. No previous history of hypertension, weakness, anorexia, vomiting, abdominal pain, fever, diarrhoea, polyuria or polydipsia.

On examination, patient pulse rate was 90/min, BP- 110/70 mmHg, mild pallor present. There was no moon facies, hirsutism, acne, purple abdominal striae, acanthosis nigricans, or mucosal pigmentation. Her systematic examination was normal. Per abdomen examination was found to be normal with no evidence of mass palpable per abdomen.

Complete hemogram done with Hb-7.4 and peripheral smear showed microcytic hypochromic anemia. Other laboratory parameters, liver and kidney function test, serum electrolytes and plasma calcium levels, thyroid function tests were normal. No abnormalities in echocardiogram and chest X-ray. Biochemical tests to determine the adrenal hormone levels were found to be normal depicted in table below.

CT abdomen and pelvis revealed 6.2×6.1×5.4 cm sized well defined heterogenous lesion with internal cystic areas seen in right adrenal region abutting upper pole of right kidney. No calcifications or fat density seen within. Left adrenal gland, bilateral kidneys and Gerota fascia are normal. MRI abdomen and pelvis showed well defined, solitary, T1/T2 heterointense focus measuring 5.6×5.6×5.3 cm with no areas of DWI restriction is seen involving the right adrenal gland. No areas of haemorrhage seen within. CT and MRI images depicted below.

Proceeded with right adrenelectomy. Intraoperative finding was right adrenal mass of size 7×6×6 well defined, solid mass without any infiltration to right kidney or Gerota fascia. Intra-operative image depicted below.

Histopathological section studied showed neoplasm composed of cells arranged in large nests and sheets separated by fibrovascular septa. The cells are round to polygonal with moderate to abundant amphophilic cytoplasm, round to oval vesicular nuclei with moderate atypia. The nuclei exhibiting stipple chromatin and prominent nucleoli.

The intervening stroma shows haemorrhage and congested blood vessels. Focal areas of necrosis seen. Capsular invasion, periadrenal adipose tissue, lymphovascular invasion absent. No mitosis made out and all these features suggestive of pheochromocytoma. Histopathological image depicted below.

Table 1: Biochemical tests to determine the adrenal hormone levels.

Investigations	Value	Normal range	Interpr-etation
ACTH (pg/ml)	46.8	<46	Near normal
Aldosterone (ng/dl)	11	1.7-23.6	Normal
Cortisol (µg/dl)	3.88	2.88-10.5	Normal
DHEA (µg/dl)	19.3	19-231	Normal
Testosterone (ng/dl)	12.25	12.09-59.46	Normal
Plasma metanephrines (pg/dl)	36.0	<60	Normal
24 hrs urinary metanephrines (mg)	0.37	<1.0	Normal
24 hrs urinary VMA (mg)	7.4	2-13.2	Normal

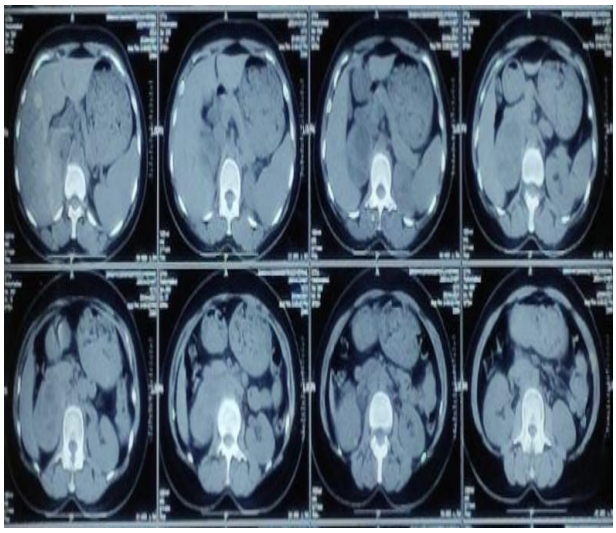

Figure 1: CT images showing right adrenal mass.

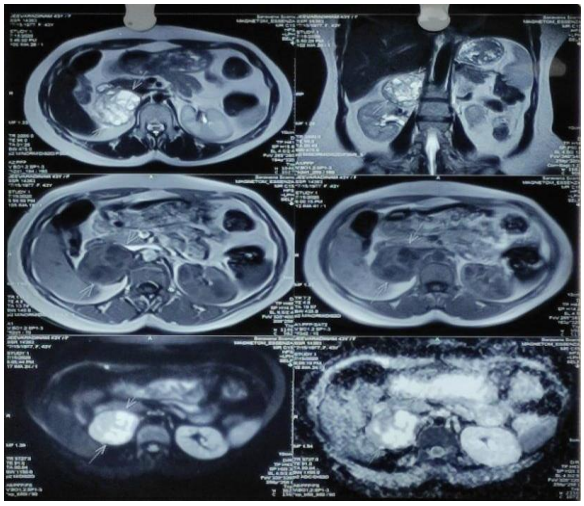

Figure 2: MRI images depicting right adrenal lesion.

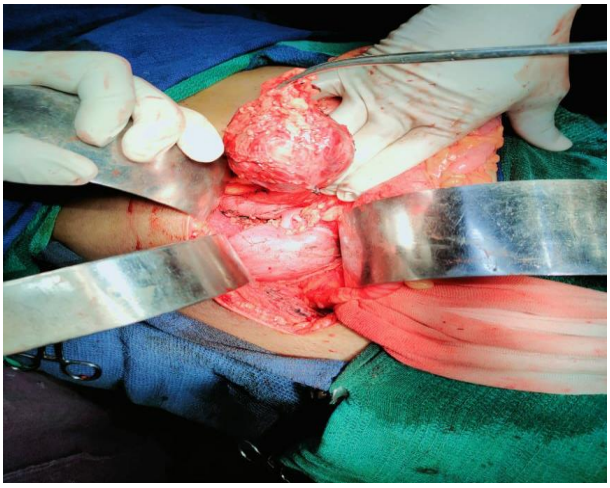

Figure 3: Intra-operative right adrenelectomy image.

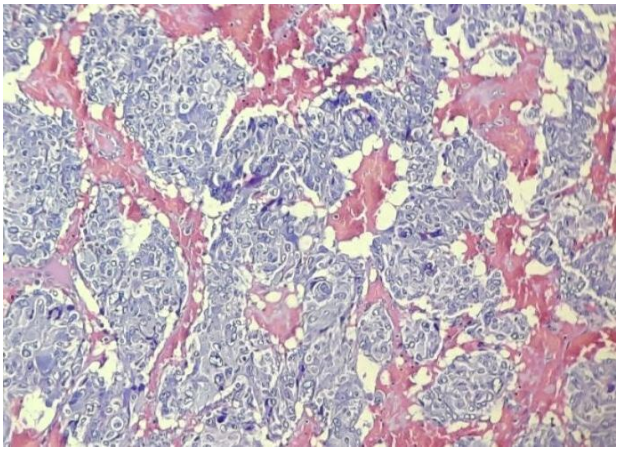

Figure 4: Histopathological image showing features suggestive of pheochromocytoma.

DISCUSSION

Pheochromocytomas are tumours of adrenal medulla which are derived from chromaffin cells and produce catecholamines. The widespread use of radiological investigations has increased the detection of adrenal incidentalomas in individuals over 30 years of age. The clinical parameters that need to be considered include functionality and aggressiveness.[2] An identification of the functionality of cortisol, aldosterone, and catecholamine and androgen secretion is essential, and here all of these parameters were within normal limits.

A CT scan with contrast-enhanced images and an MRI scan are used to localise adrenal pheochromocytomas. Metaiodobenzylguanidine (MIBG) and Positron emission tomography (PET) scanning are largely reserved for an extra-adrenal paraganglioma or particularly large tumours to rule out metastasis. In PET scanning, the Gallium-DOTA-TOC/NOC and DOPA-PET were found to perform better than FDG-PET in detecting the paragangliomas. Heterogeneity, a high Hounsfield density on a CT (more than 10 HU), a marked enhancement with intravenous contrast and delayed contrast washout (less than 60% at 10 min), a high signal intensity on a T2-weighted MRI, and cystic or haemorrhagic changes indicate a pheochromocytoma, adrenocortical carcinoma, or metastasis. However, a pheochromocytoma with lipid degeneration can result in low attenuation scores (less than 10 HU) and more than 60% washout in delayed CT scanning.[3,4] Incidental pheochromocytoma of less than 1 cm in size has no symptoms.[5] Our patient, who had a much larger mass, had no symptoms or signs of the disease. Possible reasons for this finding include the following: (i) the presence of a smaller piece of functional tissue, (ii) the release of a small amount of unmetabolised catecholamines due to a rapid intratumoural turnover rate, (iii) episodically secreting tumours, (iv) silent stress-activated tumours, and (v) false negative results due to the high-temperature handling of the laboratory specimen.

The biochemical diagnosis of a pheochromocytoma is made by measuring the 24-hrs urinary fractionated metanephrines (98% sensitivity and 98% specificity) and fractionated catecholamines.[6] There is a high specificity for the 24-hrs urinary vanillylmandelic acid (95%) and the 24-hrs urinary total metanephrines (99%). The plasma metanephrines are the preferred screening test for patients who are considered to have a high risk for a pheochromocytoma and for those suspected of having a familial form. Because the free metanephrines are formed extraneuronally, and to a large extent within the chromaffin tissues (e.g., the adrenal medulla and pheochromocytomas), these metabolites are also the more sensitive markers for a pheochromocytoma than the other catecholamine metabolites that are derived mainly from neuronal sources. Other tests, including plasma catecholamines and 24-hrs urinary catecholamines, have a poor diagnostic accuracy. Malignant pheochromocytomas are histologically and biochemically similar to benign ones. The presence of a malignant pheochromocytoma is indicated by local invasion or distant metastases, which may occur as long as 20 years after a resection.[7] Thus, even when pheochromocytomas or paragangliomas are considered benign on a pathological examination, a long-term follow-up is indicated for all patients to confirm that diagnosis. Other markers for a malignancy are an absent or weak expression of the inhibin/activin βB subunit and the presence of the SDHB subunit.[8] In the absence of any invasion, we considered the mass in our patient to be benign.

Approximately 15%-20% of patients with catecholamine secreting tumours have a germline mutation in genes such as SDHB, SDHC, SDHB (familial paraganglioma), RET (MEN 2 A and B), MENIN (MEN-1), NF-1 (neurofibromatosis), and VHL (von Hippel-Lindau syndrome). Bilaterality, a family history of pheochromocytoma, younger age (20 years or below) genetic testing is necessary.[9,10] In our patient, the factors of age of presentation, a unilateral pheochromocytoma, and the absence of a family history supported the decision against a familial origin. Pre-operatively α-adrenoreceptor

blocker (phenoxybenzamine) is used to block catecholamine excess and its consequences during surgery. With adequate medical pretreatment, the perioperative mortality rate has decreased from 20-45 per cent to less than 3 per cent. A dose of 20 mg of phenoxybenzamine initially, increased daily by 10 mg until a daily dose of 100-160 mg is achieved and the patient reports symptomatic postural hypotension. A laparoscopic removal is commonly performed. A laparotomy is reserved for larger tumours and that show local invasion.[11] Both of these approaches are equally successful in terms of overall survival. The greatest intra-operative concern is a release of catecholamines leading to life-threatening hypertension. Hypertensive crises can cause myocardial infarction, heart failure, dysarrhythmia, and cerebral haemorrhage. Severe hypertension can occur at any time during the surgery, but the induction, intubation, and tumour palpation lead to greatest catecholamine release.

Following early ligation of the vein that drains the pheochromocytoma, intravenous fluid administration is essential for volume expansion. The sudden drop in catecholamines can lead to significant hypotension, which requires aggressive fluid replacement with a combination of crystalloids and colloids. Pressors may be necessary to maintain blood pressure in severe hypotension, but they are best avoided and are contraindicated if the patient is hypovolaemic.[12] Often, the hypotension of a pheochromocytoma is refractory to agents such as norepinephrine, epinephrine, and dopamine because of the desensitisation of the sympathetic receptors to the previous persistently high levels of catecholamines. Patients should be observed for 24 hrs in the intensive care unit as hypovolaemia and hypoglycaemia may occur. Lifelong yearly biochemical tests should be performed to identify recurrent, metastatic or metachronous phaeochromocytoma.

CONCLUSION

Pheochromocytoma is a clinically important disorder because it leads to high morbidity and mortality rates if untreated. Fractionated metanephrines and catecholamines in a 24 hrs urine analysis is the preferred biochemical test. In a biochemically silent pheochromocytoma, characteristic CT findings should identify its possible presence. A combination of anatomical imaging studies (CT or MRI) with functional imaging studies (MIBG and PET) is used to locate adrenal, extra-adrenal, recurrent, and metastatic tumours. An adequate α and β blockade should be ensured before proceeding to tumour removal. For individuals with adrenal tumours larger than 4-6 cm, a surgical resection is appropriate. However, for a pheochromocytoma, surgery is recommended irrespective of the size and is even recommended in case of normal biochemical study to prevent future complications.

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