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Case Report

Pathology Section

Biochemically Silent Pheochromocytoma Presenting with Left Flank Pain and Constipation: A Rare Case Report

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ABSTRACT

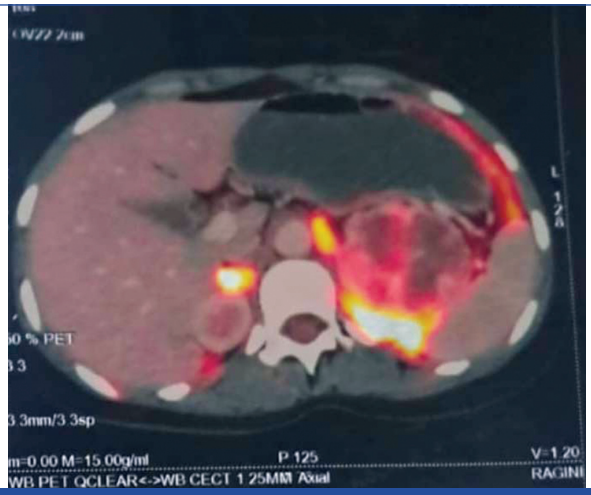
The adrenal glands each have two zones: the cortex and the medulla. Adenomas and carcinomas are tumours arising from cortex whereas pheochromocytomas and neuroblastomas arise from medulla. Hypoplasia, hyperplasia, cytomegaly, cysts, nodules and accessory tissue are some of the Non-neoplastic lesions of adrenal gland. Adrenal Incidentaloma (AI) or adrenal lesion discovered radiologically is very rare. We report a case of AI with the evidence of pheochromocytoma in 22-year-old female who presented with atypical symptom of left flank pain and constipation with a negative history for sweating, hypertension, chest pain, weight gain, excess hair growth on the body, acne, menstrual irregularity and normal Blood Pressure (BP) finding throughout the course of illness. Biochemical parameters for adrenal hormone were within normal limits. The mass was excised and sent for histopathological examination. The diagnosis of pheochromocytoma was made which was confirmed on immunohistochemistry. PASS scoring was done. IHC was strongly positive for synaptophysin and chromogranin and negative for calretinin and inhibin. Though pheochromocytoma has variable clinical manifestation and diagnosis is usually established by strong clinical suspicion, measurement of catecholamines and its metabolites along with radiographic localisation and histopathological confirmation of excised mass. Malignant potential of pheochromocytoma is only established by metastasis, long-term follow-up in patients after resection is necessary. Our case presents as a diagnostic challenge because of normal biochemical investigation and rare presentation. Surgery is recommended irrespective of size and normal biochemical study to prevent complication.

Keywords: Catecholamines, Histopathology, Radiographic

CASE REPORT

A 22-year-old female presented to the surgery Outpatient Department (OPD) with chief complaints of left flank pain for one month, which was insidious in onset and gradually increasing in intensity associated with nausea, anorexia, and constipation. Routine painkiller was taken for the pain. Her general physical and systemic examinations were within normal limits. Blood Pressure (BP) was normal throughout. There was no history of any chronic disease. Plain CT scan of abdomen and pelvis revealed a heterogenous mass lesion measuring 48×55 mm in the left supra renal region with central calcification, suggestive of a left adrenal mass, likely adenoma versus pheochromocytoma. Further, contrast-enhanced CT revealed that the lesion was enhancing in intensity on the arterial phase with few non-enhancing necrotic areas and a calcific focus within. The left adrenal gland was not visualised separately. Findings were suggestive of pheochromocytoma; however, she gave a negative history for sweating, hypertension, chest pain, weight gain, excess hair growth on the body, acne, menstrual irregularity, diarrhoea, polyuria, or polydipsia. Her family history was also non-contributory. Positron Emission Tomography-Computed Tomography (PET-CT) revealed a metabolically active, enhancing soft tissue density mass lesion measuring 5.3×5.9 cm, maximum Standardized Uptake Value (SUVmax) 12.5 in the left supra renal region, areas of necrosis noted. The left adrenal gland was not visualised separately. Fat planes with the pancreas and spleen were preserved. No other hypermetabolic focus was noted in the rest of the visualised body which excluded the presence of metastatic disease or multiple chromaffin tumours [Table/Fig-1]. There was no evidence of moon facies, hirsutism, acne, purple abdominal striae, acanthosis nigricans, or knuckle or mucosal pigmentation.

Complete haemogram revealed haemoglobin of 9.3 g/dL, with peripheral smear showing normocytic normochromic anaemia. Other laboratory parameters, liver and kidney function tests, were within normal limits. Biochemical tests for adrenal hormone were normal [Table/Fig-2]. Patient was kept nil per oral since midnight with intravenous infusion of one unit ringer lactate. On the day of surgery, tablet prazosin was administered in the early morning, followed by injection ceftriaxone (Monocef) 1 g just before surgery. BP was continuously monitored, and part preparation was completed. Intraoperative period was uneventful. Postoperative biochemical tests for adrenal hormone were normal [Table/Fig-3]. The mass was excised and sent to the department of pathology for histopathological examination. Grossly, one globular yellowish white soft tissue piece with attached fibro-fatty tissue measuring 5×3.5×1 cm was received with cut surface showing well-circumscribed yellow to dark brown areas [Table/Fig-4]. Histopathological examination showed encapsulated tissue showing tumour cells arranged in nests, separated by thick fibrovascular septa. Individual cells are oval to polygonal with granular amphophilic to clear cytoplasm, fine chromatin and prominent nucleoli at places. At places cell with highly



[Table/Fig-1]: PET-CT revealed a metabolically active enhancing soft-tissue density mass lesion measuring 5.3×5.9 cm, SUVmax 12.5 in the left supra renal region.

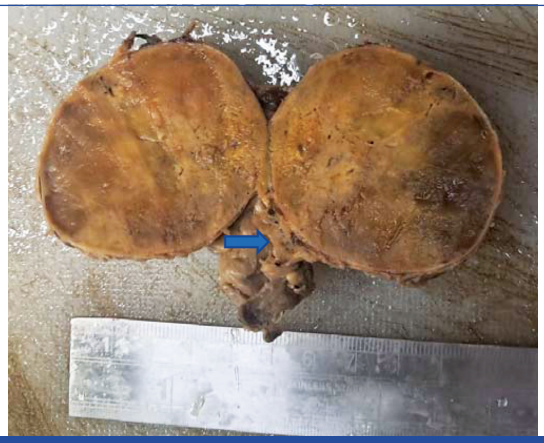
pleomorphic hyperchromatic nucleus was also noted. There was no invasion of peri-adrenal adipose tissue. A normal adrenal gland was identified at the periphery [Table/Fig-4,5]. Mitotic figures and areas of haemorrhage were not identified. Pheochromocytoma of the Adrenal gland Scaled Score (PASS) score is 2. Histopathological features were suggestive of pheochromocytoma which was confirmed by immunohistochemistry. Immunohistochemistry was strongly positive for chromogranin and synaptophysin and negative for calretinin and inhibin, confirming the diagnosis of pheochromocytoma. Positive internal controls for Chromogranin is appendix and for synaptophysin is islets of pancreas [Table/Fig-6-8].

Investigation	Value	Normal range	Interpretation
Plasma ACTH (pg/mL)	44	7.3 -65	Normal
Plasma Aldosterone (ng/dL)	32.5	3.1-35.4	Normal
Plasma cortisol (µg/dL) at 8:00 am	12.8	10-20	Normal
Plasma Cortisol (µg/dL) Overnight Dexamethasone Suppression Test (ONDST)	2.1	< 5	Normal
24 hours urine fractioned metanephrines (mg)	0.1	<1	Normal
Plasma metanephrines (µg/dL)	5	<100	Normal
24-hour urinary Vanillylmandelic Acid (VMA) (mg/24 h)	1.6	8-12	Normal

[Table/Fig-2]: Biochemical tests to determine the adrenal hormonal levels (pre-operative).

Investigation	Value	Normal range	Interpretation
Plasma ACTH (pg/mL)	38	7.3 -65	Normal
Plasma Aldosterone (ng/dL)	28.8	3.1-35.4	Normal
Plasma cortisol (µg/dL) at 8:00 am	10.8	10-20	Normal
Plasma cortisol (µg/dL) Overnight Dexamethasone Suppression Test (ONDST)	1.1	<5	Normal
24 hours urine fractioned metanephrines (mg)	0.1	<1	Normal
Plasma metanephrines (µg/dL)	3.5	<100	Normal
24-hour urinary Vanillylmandelic Acid (VMA) (mg/24 h)	1.0	8-12	Normal

[Table/Fig-3]: Biochemical tests to determine the adrenal hormonal levels (postoperative).



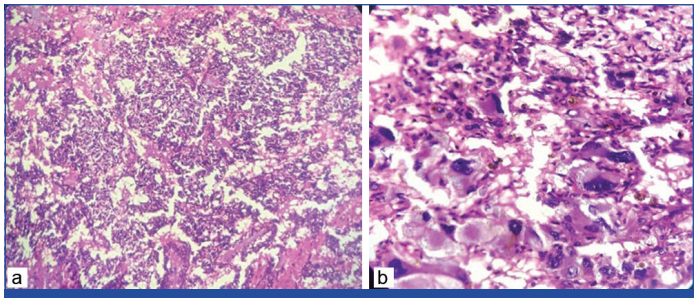
[Table/Fig-4]: Gross macroscopic appearance of left adrenal mass, cut surface showing well circumscribed yellow to dark brown areas, with normal appearing adrenal gland at periphery (arrow).

Following surgery patient showed full recovery and showed no symptoms or complications in follow-up for three months.

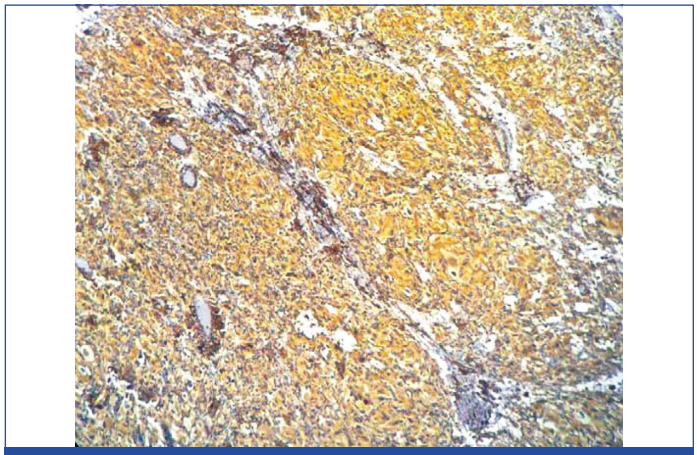
DISCUSSION

Pheochromocytoma and neuroblastoma arise from adrenal medulla, whereas adenomas and carcinomas arise from adrenal cortex [1].

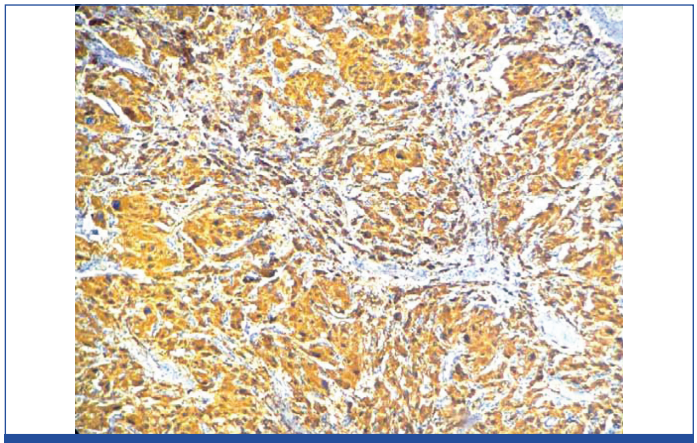
An adrenal gland lesion that is identified during a radiological investigation for a reason other than adrenal disease is termed an



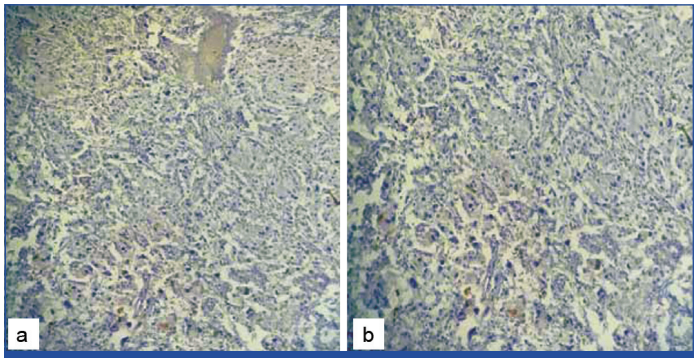
[Table/Fig-5]: a) showing tumour cells predominantly arranged in nests, separated by thin fibrovascular septa and occasional cords and sheets, (H&E, 10x); b) shows individual oval to polygonal cells with granular amphophilic to clear cytoplasm with occasional cells showing marked pleomorphism (H&E, 40x).



[Table/Fig-6]: Shows positivity for chromogranin (IHC, 10x).



[Table/Fig-7]: Shows positivity for synaptophysin (IHC, 10x).



[Table/Fig-8]: Shows negative for calretinin and inhibin (IHC, 10x).

Adrenal Incidentaloma (AI). Patients with AI must be evaluated for hyperaldosteronism, pheochromocytoma and hypercortisolism [2]. Pheochromocytoma are catecholamines producing tumours arising from chromaffin cells and accounts for 0.1-0.6% in prevalence and 80-85% arise from adrenal medulla [3,4].

Catecholamines produced include epinephrine, norepinephrine, dopamine and their metabolites metanephrines, normetanephrine, or methoxytyramine producing spectrum of clinical symptoms such as,

sustained or episodic hypertension, headache, palpitations, sweating and pallor [2,4]. Laboratory diagnosis of pheochromocytoma is usually achieved by measuring metabolites in plasma and urine especially total and fractionated metanephrines [5].

Pheochromocytoma are derived from chromaffin cells of adrenal medulla producing catecholamines [3,6]. Approximately, 5.0-6.5% cases of AIs are pheochromocytoma [7]. The detection rate of AIs has increased due to the extensive use of radiological investigation. Functionality of tumour in terms of catecholamines, aldosterone, and cortisol levels, along with aggressiveness, are clinical parameters that need to be evaluated [6,7]. Incidental pheochromocytoma is usually smaller in size measuring approximately less than 1 cm, with no obvious sign or symptom [8]. Both biochemical confirmation of excess catecholamines or its metabolites production and radiological investigation are required for detecting the tumour along with knowledge regarding the classical and non-classical presentation is important. Since catecholamines have short half-life and is rapidly metabolised by enzyme Catechol-O-Methyltransferase (COMT), hence for diagnosing adrenal pheochromocytoma measuring increased metanephrines and normetanephrine and adrenal paragangliomas measuring normetanephrine is preferred [5]. A 24-hour urinary vanillylmandelic acid and 24-hour urine total metanephrines are considered to have high specificity [3,4].

We report a rare case of AI which was diagnosed as pheochromocytoma in a 22-year-old female with unusual biochemical and clinical expression. There were two unusual findings in this patient, firstly absence of hypertension, palpitation, or sweating, and secondly normal level of plasma catecholamines. Approximately 8% of patients with pheochromocytoma are completely asymptomatic. Additionally, plasma and urinary catecholamine concentrations are normal in about 8-9% of patients with sporadic paragangliomas and 21-31% of those with hereditary paragangliomas [4]. Possible causes for the findings include: a) functional tissue is small; b) due to high intratumoural turnover unmetabolised catecholamines are released; c) false negative results due to improper handling of specimen; d) episodically secreting tumours; e) silent stress activated tumours [3,5].

A CECT and MRI scan are used to localise adrenal pheochromocytoma [9]. Certain imaging features such as, large size (more than 6 cm), irregular margins, delayed wash out on CECT, calcification, and high unenhanced CT attenuation values (more than 10 Hounsfield) favour malignancy [4]. Some histologic features can cause problems in differential diagnosis. Paragangliomas may have spindle cell morphology or contain pigment, requiring distinction from mesenchymal tumours and melanoma, respectively. Extensive degenerative change in pheochromocytoma may mimic adrenal cortical tumour [10]. A periodic follow-up for blood pressure is needed. Annual biochemical testing to assess metastatic disease, tumour recurrence, or delayed appearance is recommended [4].

Though biochemically silent and with rare symptoms of left flank pain and constipation, histopathological examination aided in the diagnosis of pheochromocytoma in our case, which was confirmed on immunohistochemistry.

The only clue pointing towards malignant potential of pheochromocytoma is local invasion or distant metastases hence even a benign pathology report of pheochromocytoma requires long term follow up in patients after resection to confirm the diagnosis [11].

In cases with bilaterality, positive family history, or younger age at presentation (≤20 years), genetic testing for germline mutations in Succinate Dehydrogenase complex subunit A (SDHA), SDHB, SDHC, SDHD, rearranged during transfection proto-oncogene (RET), Neurofibromin 1 (NF1), protein kinase cAMP-dependent type I regulatory subunit alpha (PRKAR1A), and von Hippel-Lindau tumour suppressor (VHL) should be performed [4,5,12]. However, no genetic testing was done in our case. Though biochemically silent pheochromocytoma has been reported earlier, this is one of the rare cases of an incidentaloma that was diagnosed as pheochromocytoma presenting as flank pain and constipation as primary symptoms.

CONCLUSION(S)

In absence of classical signs, symptoms and biochemical findings, a high degree of clinical suspicion, radiological and histopathological confirmation, is required to diagnose a case of pheochromocytoma presenting as an AI. A periodic follow-up in form of regular blood pressure measurement, annual biochemical testing to is required to asses metastatic disease.

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