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Case Report

A Very Large Asymptomatic and Biochemically Negative Incidentaloma Further Diagnosed as Pheochromocytoma: A Case Report

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Abstract

Background: Pheochromocytoma and Paraganglioma can secrete excess Catecholamines, causing hypertension, tachycardia, hyperhidrosis, or shock. Measuring blood and urine Metanephrine levels helps with a proper diagnosis. Tumor localization can be performed using Magnetic Resonance Imaging (MRI) or Computed Tomography (CT). Tumors can also present as an asymptomatic adrenal incidentaloma, identified radiographically. Here, we report one such interesting case.

Case report: A 48-year-old woman was referred to us with an 8.9 × 9.4 cm right adrenal incidentaloma, as measured by computed tomography (CT) scan. She was totally asymptomatic, with normal blood pressure both before and after the operation. Repeated biochemical screening remained within normal range. The patient underwent right adrenalectomy (via a subcostal incision), and histological findings confirmed Pheochromocytoma.

Conclusion: This case illustrates how radiologic findings in an asymptomatic and biochemically negative patient can alert to the presence of a Pheochromocytoma.

Keywords: Pheochromocytoma, Incidentaloma, Hypertension, Biochemically negative, Asymptomatic, Computed tomography, Magnetic resonance imaging

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Introduction

Pheochromocytomas and Paragangliomas, the two types of Chromaffin cell tumors, are derived from the sympathetic or parasympathetic Paraganglia located in adrenal or extra-adrenal tissues. They were previously thought to be biochemically and clinically active, but recent studies have suggested that these tumors show a wide spectrum of cellular and biochemical attributes ranging from aggressive metastasis potency to complete biochemical inactivity (1,2).

Pheochromocytoma and Paraganglioma can be seen in about 0.2 to 0.6% of the hypertensive population in outpatient clinics; however, these conditions are demonstrated to be underdiagnosed since autopsy studies showed missed tumors in 0.05–0.1% of the general deceased population. A little less than 2% of the hypertensive children are afflicted with pheochromocytoma, and about 5% of the incidentalomas in the adrenal gland are further discovered to be pheochromocytoma (1).

Excess release of catecholamines is responsible for the symptoms, including Headache, Sweating, Palpitations, Nervousness, anxiety, Flushing, Tremors, Chest pain, Nausea, vomiting, and Warmth or heat intolerance (3). The diagnostic tools for early detection of pheochromocytoma include the measurement of fractionated metanephrine in 24-hour urine and the plasma free Metanephrine levels. Furthermore, radiologic modalities like CT and MRI can be used to localize the tumors (4, 5). The tumor can be asymptomatic and identified only radiologically in some cases. Herein, we report an interesting case in this regard.

Case Report

A 48-year-old woman was referred to us by an endocrinologist with a huge mass in her right adrenal gland. She had no sign of hypertension, and her physical examination was normal (Adrenal Incidentaloma).

The biochemical assessments were as follows:

Urine Metanephrine (µg/24 hr) 500 microgram/24

hrs urine with a normal range within 140 to 785 microgram/24 h, Vanillylmandelic acid (mg/24 hr) 3.1 mg/24 h with a normal range within 0 to 6 mg/24 h, urine Normetanephrine (24 hrs) 221 µg/24 hr with a normal range within 75 to 375 microgram/24 h, DHEAs 0.45 µmol/l with a normal range up to 6 µmol/l, Aldosterone 11 ng/dl with a normal range within 3 to 25 ng/dl, and Renin 28.5 mIU/ml with a normal range within 7 to 30 mIU/ml; All were in normal laboratory range. Repeat of biochemical evaluations was also in the normal range.

CT scan showed an 8.9×9.4 cm multicystic right adrenal mass. The mass enhancement was increased after injecting the contrast material, with attenuation between 30 and 60 Hounsfield Units (HU). Non-contrast attenuation and formal washout percentage were not available (Figure 1).

Abdominal MRI with contrast showed a 9.5×10 cm solid and necrotic right adrenal mass. IVC and the para-aortic region were intact, and no hepatic metastasis was seen (Figure 2).

We did not have access to functional imaging (MIBG PET/CT) at our center.

We did not perform germline testing since the patient did not consent to doing so due to financial considerations.

Given repeatedly negative biochemistry and normal blood pressure, we consulted endocrinology. The consensus was that preoperative alpha-blockade was not required. The patient underwent pre-operative hydration and careful intraoperative monitoring. Then, she underwent right Adrenalectomy via a subcostal incision.

On histopathological evaluation, the neoplastic cells were polygonally arranged as small nests separated by delicate, highly vascularized connective tissue stroma (ZellBallen pattern of pheochromocytoma). The cytoplasm was abundant and eosinophilic. The nuclei were round or oval with occasionally prominent nucleoli. The immunohistochemical examination showed a positive reaction for synaptophysin and chromogranin. Ki67 labeling index was 6% (Figure 3). S100 immunostaining was not performed.

At six-month and one-year follow-up, the patient was still asymptomatic, and both plasma and urinary Metanephrines were within reference ranges. No radiologic evidence of recurrence was observed.

Discussion

The patient was a biochemically negative asymptomatic individual with an incidentaloma, and the radiologic findings showed an incidentaloma that was further diagnosed as Pheochromocytoma only after adrenalectomy.

The early and accurate diagnosis of pheochromocytoma is important due to its potentially lethal nature, and

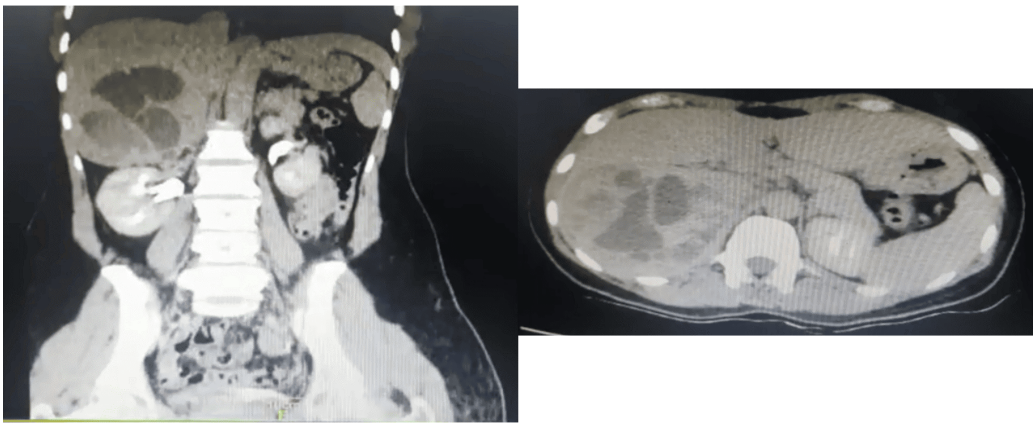

Figure 1. Contrast-enhanced abdominal CT scan showing a right multicystic adrenal mass

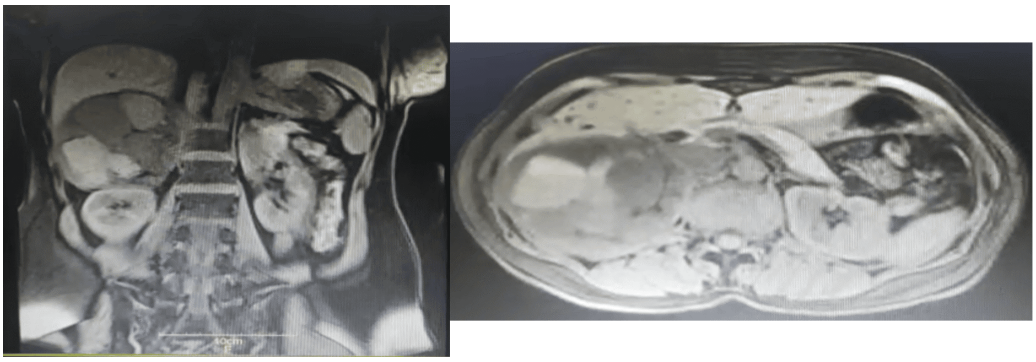

Figure 2. Contrast-enhanced abdominal MRI depicting a solid-necrotic adrenal mass

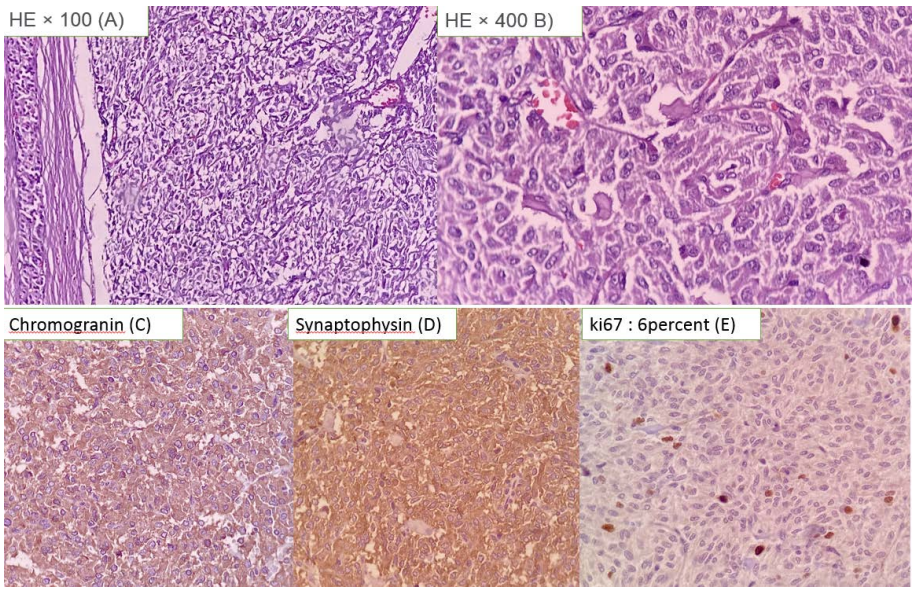

Figure 3. Histopathology and immunohistochemistry. (A, B) Well-circumscribed tumor with Zellballen architecture. (C, D) Diffuse positivity for synaptophysin and chromogranin staining. (E) Ki-67 labeling index of 6%

since hypertension in patients can be cured only with an accurate knowledge of its context. Hypertensive crisis or shock can be caused by specific medications, including anesthetic agents, as well as parturition and surgical interventions. It is worth noting that some cases might appear symptom-free. Such patients are at risk for poor outcomes (6).

Although many centers favor empiric alpha-blockade when imaging suggests PPGL, the decision can be individualized. In this case, after consulting endocrinology, we proceeded without alpha-blockade, prioritized hydration, and observed stable intraoperative hemodynamics. We do not suggest this as a general rule; rather, it reflects individualized risk assessment in a biochemically negative, normotensive patient.

One's evaluation method, as well as the target population (which cases should undergo evaluation), can cause different outcomes in terms of prevalence. Age is also another factor as Adrenal Incidentaloma is higher in the elderly (7).

In a study on 42 cases with adrenal incidentaloma and mildly elevated Metanephrines in urine or plasma who were treated between 1995 and 2005, 30% were ultimately diagnosed with pheochromocytoma. The study showed that 30% of these patients had Pheochromocytoma (8).

Although an incidental pheochromocytoma with less than 1 cm in diameter can be asymptomatic (9), in this case, the mass was much larger, but interestingly, the patient was symptom-free. A few conceivable reasons behind this finding include:

- The functional piece of the tumor is small in size.
- Secretion of only a small amount of unmetabolized catecholamines due to a rapid intratumoral turnover rate
- Catecholamine is secreted episodically.
- The tumor might be silent and stress-activated.
- False-negative results due to pre-analytical errors as warm temperature during laboratory specimen handling or ingestion of caffeinated beverages in the 24 hours preceding the test.
- Ineffective catecholamine biosynthesis (10, 11)

CT and MRI can be used as localization tools (5). The discovery of adrenal incidentalomas has increased since the use of these tools. 3% to 4% of abdominal CT and MRI studies reveal an adrenal incidentaloma. These incidentalomas are mostly adenomas, and other types of adrenal mass include pheochromocytomas, myelolipomas, cysts, metastases, and adrenocortical carcinomas. Patients with incidentalomas are usually asymptomatic, but the mass may later become functional (12-14).

Imaging findings indicating pheochromocytoma and malignant neoplasms include high Hounsfield density (more than 10 HU) on CT, marked enhancement after intravenous contrast injection with delayed contrast washout (less than 60% at 10 minutes). These structures appear heterogeneous with hemorrhagic or cystic changes. A high signal intensity on a T2-weighted MRI is additionally suggestive of pheochromocytoma or malignant lesions. However, pheochromocytomas with lipid degeneration can result in a lower attenuation score (less than 10 HU) and more than 60% washout in delayed CT scanning that would make them appear similar to adrenal adenomas (9).

In this case, CT showed an 8.9 × 9.4 cm multicystic right adrenal mass. The mass enhancement was increased after

injecting the contrast material. Attenuation was between 30 and 60 Hounsfield Units (HU). Abdominal MRI with contrast showed a 9.5×10 cm solid and necrotic right adrenal mass. IVC and the para-aortic region were intact, and no hepatic metastasis was seen. Functional imaging (MIBG PET/CT) was not available at our center.

The patient also did not undergo germline testing due to its cost.

The size of Pheochromocytomas was 4.9 cm on average at the time of diagnosis. It is also worth noting that tumor sizes are directly correlated with hormone levels, independent of the patients' signs and symptoms. Although larger tumors could secrete any amount of catecholamines, smaller tumors mostly produce lower levels of catecholamines. This difference in hormone secretion would have resulted from structural differences, including cystic degeneration or necrosis of the tumor, in addition to dissimilarity in hormone metabolism. Hormone metabolism within the tumor itself can also lead to a variation in its release. More than 90% of the elevated fractionated plasma Metanephrines in pheochromocytoma patients result from hormone metabolism within the tumor cell and not peripheral metabolism (15, 16). Thus, in our presented case, one other probable reason behind her normal lab findings might be the necrosis seen in the imaging.

Our case did not undergo functional imaging and germline testing. Of course, a case report limits generalizability.

Conclusion

This case shows that even though there is a positive correlation between the tumor size and the catecholamine excretion, there is always a chance that even a large biochemically negative tumor would finally be diagnosed as a pheochromocytoma; therefore, precautions should always be taken.

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Authors' Contribution

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Investigation: Mohammadamin Hesamarefi.
Methodology: Reza Mohammadi.
Project administration: Reza Mohammadi.
Resources: Mohammadhadi Hesam-Arefi.
Software: Mohammadali Bagherinasabsarab.
Supervision: Reza Mohammadi.
Validation: Mohammadali Bagherinasabsarab.
Visualization: Reza Mohammadi.
Writing–original draft: Mohammadamin Hesamarefi.

Competing Interests

The authors declare no conflicts of interest.

Data Availability Statement

The data were derived from the patient's medical records. They contain potentially identifying information; therefore, they are not publicly available. However, if reasonably requested, anonymous data can be provided by the corresponding author.

Ethical Approval

The patient was asked to sign an informed consent form for her clinical information to be published while remaining anonymous. We removed all potentially identifying information, and the report was in concordance with the principles of the Declaration of Helsinki.

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