

## Diagnostic Enigma: A Case of Silent Pheochromocytoma in a Woman

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### Abstract

Pheochromocytomas are rare tumours that arise from neural crest cells of the adrenal medulla. They commonly secrete catecholamines and other biological peptides that account for, hypertension, palpitations, and episodic headaches associated with the condition. However, the symptoms and clinical presentations are highly variable due to variations in catecholamine biosynthesis and secretion because of differences in gene expression. A small proportion of tumours hardly synthesize or release catecholamines and may have no symptoms and are termed non-functional pheochromocytoma. The non-functional pheochromocytomas are usually identified as incidentalomas, and the biochemical workup is usually negative. Non-functioning pheochromocytomas pose a challenge even to an astute clinician. We report a woman who presented with clinically non-functioning pheochromocytoma.

**Keywords:** Pheochromocytoma, catecholamines, hypertension, non-functioning.

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## Introduction

Pheochromocytoma is a tumour that arises from the catecholamine-producing cells of the adrenal medulla. Approximately 1 to 2 per 100,000 individuals are diagnosed annually with pheochromocytoma, although the reports on incidence may vary (1). It is estimated that approximately 0.5% of cases of hypertension are due to pheochromocytoma (2). Approximately 5% of pheochromocytomas are incidentally detected as adrenal masses (3, 4). Incidentally discovered lesions account for 10% to 25% of all pheochromocytomas (2, 5).

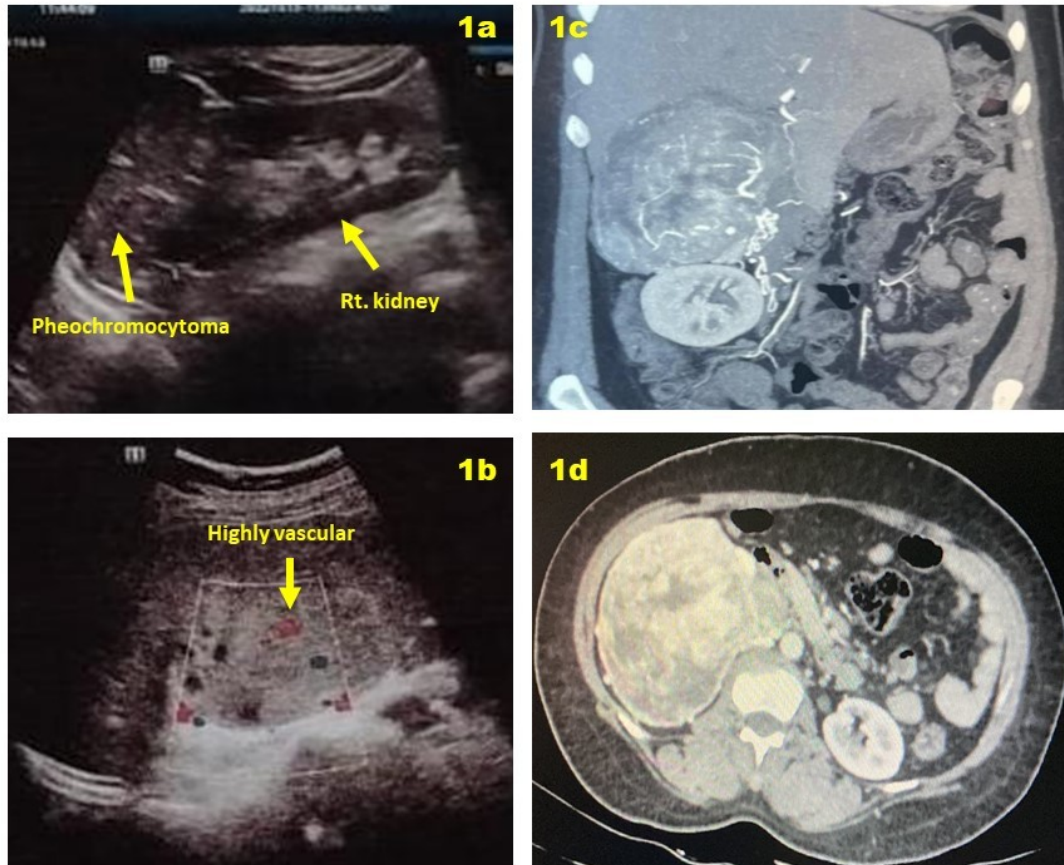
Paroxysmal hypertension is the classic presenting sign in patients with pheochromocytoma. Such episodic spikes in blood pressure are documented in only approximately 30% to 50% of patients and can occur against the backdrop of baseline essential hypertension. The remainder of patients demonstrate persistently elevated blood pressure, and a minority are entirely normotensive (6). The triad of headache, episodic sudden perspiration, and tachycardia is a classic hallmark of pheochromocytoma (5). Pheochromocytomas, due to their diverse presentations, are considered “the great mimic” and this can pose a challenge even to an astute clinician (7, 8). In this paper we report a woman who presented with clinically non-functioning pheochromocytoma.

## Case Report

A 45-year-old female was admitted to the Urologic-oncology division of the hospital with complaints of right-sided abdominal pain of two months duration. The patient did not have a known case of diabetes mellitus, hypertension or cholelithiasis. The vital parameters such as blood pressure, pulse rate and respiration were within normal range. Abdominal ultrasonography (Figure 1a, b) done at a primary healthcare centre revealed a heterogeneously echogenic large mass in the region of the right adrenal gland. The patient was referred to our hospital for further management.

A plain CT (computed tomography) abdomen confirmed the presence of a large soft tissue lesion measuring 12×9.5 cms in the right suprarenal location (Figure 1c&d), pushing the right kidney inferiorly. The right adrenal gland was not seen separately. The left adrenal gland appeared normal. MRI (magnetic resonance imaging) abdomen, revealed a well-defined lobulated lesion appearing hypointense on T1 weighted images and appeared hyperintense on T2W images. In the post-contrast study, the lesion showed heterogenous

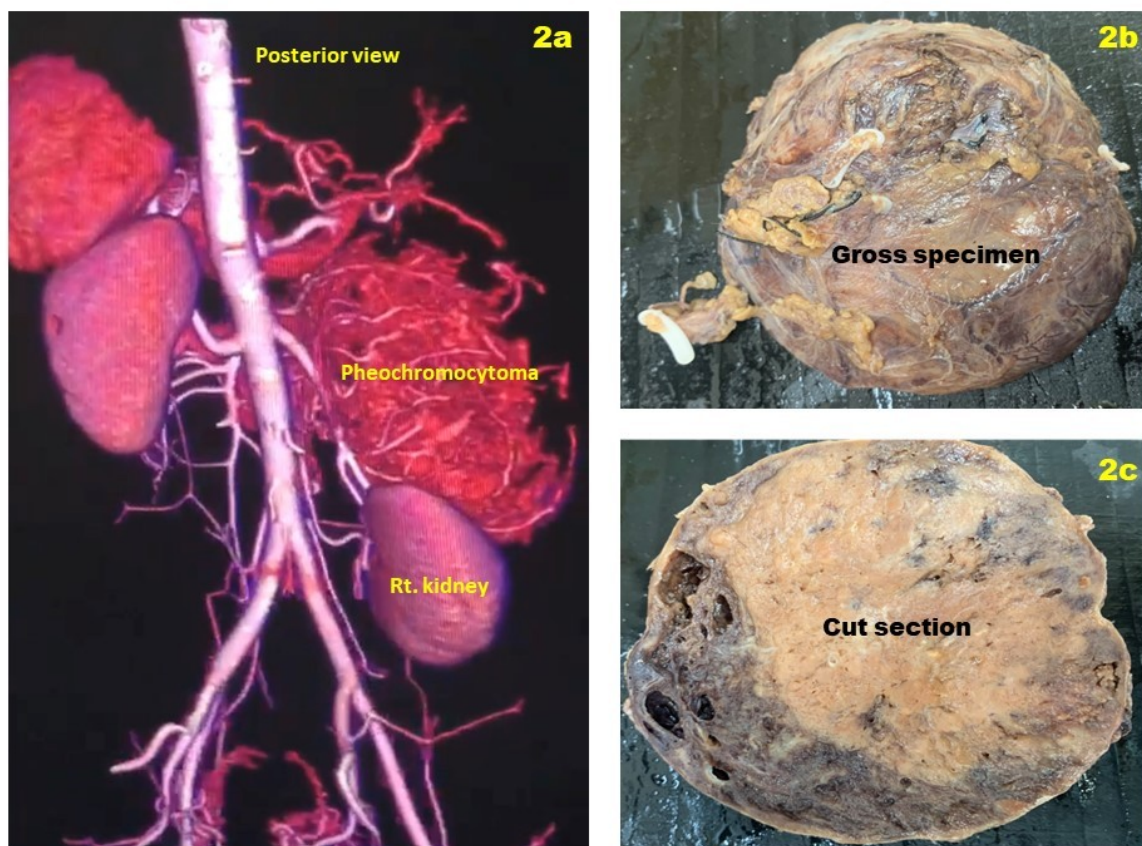
enhancement. The features were suggestive of a right adrenal pheochromocytoma. Twenty-four hours of urinary VMA (vanillylmandelic acid) excretion were within normal ranges and the serum metanephrine and nor-metanephrine levels. In view of normal catecholamine levels, a diagnosis of non-functioning pheochromocytoma or adrenocortical carcinoma was thought of.



**Figure 1. a & b:** Ultrasonography shows Rt. Kidney being pushed inferiorly by the adrenal mass. The mass appears to be highly vascular on colour doppler. **c & d:** CT scan of the abdomen shows Rt. Sided adrenal mass is 12x9.5 cm, pushing the Rt. Kidney inferiorly.

On CT angiography of the abdomen (Figure 2a), the lesion appeared well-defined, lobulated and heterogeneously enhancing with haemorrhagic and necrotic areas within it. Early arterial enhancement and washout on delayed phases were noted. The patient was properly prepared for surgery and was put on calcium channel blockers on the advice of an endocrinologist. The patient was explored using a right subcostal incision and retroperitoneal approach. The

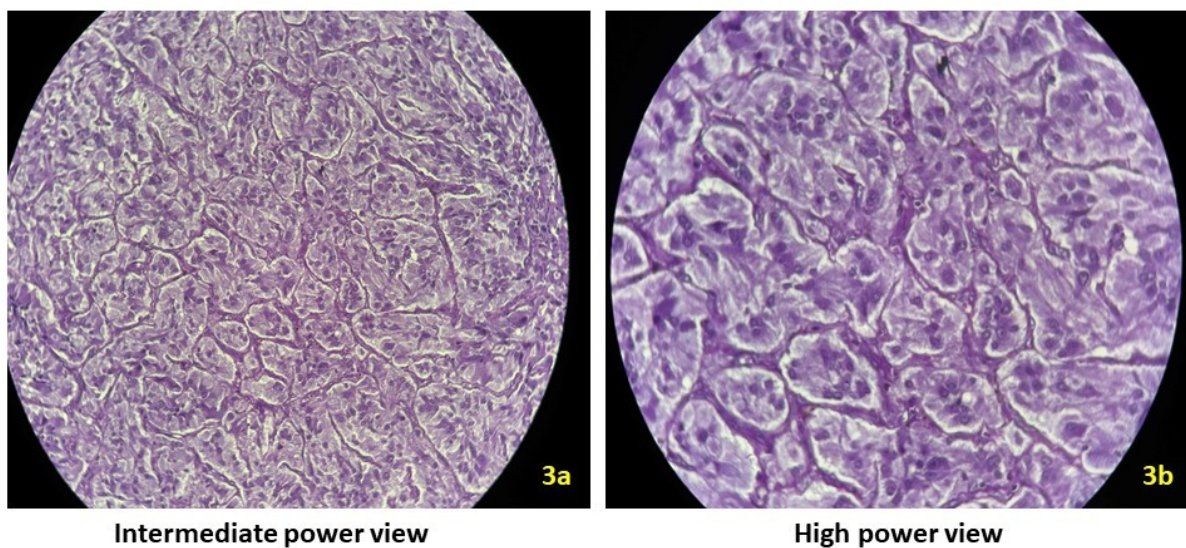
lesion was dissected away from the surrounding tissues and excised. Both the intra-operative period and the post-operative period were uneventful. There were no episodes of hypertension noted. The gross specimen (Figure 2 b&c) was of the size 12×9.5 cms and appeared to be soft and lobulated. The histopathology report shows an intermediate and power view of the histopathology specimen Zell-Ballen pattern (nesting) pathognomonic of pheochromocytoma (Figure 3 a & b).



**Figure 2. a.** CT angiography shows a highly vascular adrenal tumour with the Rt. Renal artery being encased by the tumour. **b.** Gross specimen **c.** Cut a section of the specimen mahogany brown colour tumour.

## Discussion

Pheochromocytomas are catecholamine-secreting neuroendocrine tumours that arise from the chromaffin cells of the adrenal medulla. The incidence is about 0.1% of the general population and 0.1–0.2% of patients presenting with hypertension (9). Recent advances in genetic studies have shown that up to 25% of patients have an inherited pattern with germline mutations (10, 11). Inherited Pheochromocytomas are known to be associated with conditions such as multiple endocrine neoplasia type II (MEN-2A or MEN-2B), von Recklinghausen's neurofibromatosis type I (NF-1), von Hippel–Lindau (VHL) syndrome, and familial PG (pyoderma gangrenosum) due to germline mutations of genes encoding succinate dehydrogenase (SDH) subunits B, C, and D (9).



**Figure 3. a:** Intermediate power view of the Histopathology specimen Zell-Ballen pattern (nesting) pathognomonic of pheochromocytoma. **b:** High power view of the Histopathology specimen Zell-Ballen pattern (nesting) pathognomonic of pheochromocytoma.

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Pheochromocytoma, because of its protean manifestations is often referred to as “the great mimic”. Symptoms of pheochromocytomas are due to progressive excess of catecholamines, leading to hypertension. The most consistent sign in pheochromocytomas is hypertension, <sup>[5,9]</sup> as a result of the activation of  $\alpha$ - and  $\beta$ -adrenergic receptors by catecholamine excess. Asymptomatic pheochromocytomas have been referred to as non-functional, silent or subclinical, and non-secreting lesions (9, 12). Absence of hypertension has been reported in 14–55% of incidental pheochromocytomas (13-15), especially those with adrenal incidentalomas and dopamine-secreting tumours.

Recent studies have shown that pheochromocytomas that are normotensive show downregulation of five genes phenylethanolamine-*N*-methyltransferase (PNMT), secretogranin II, vesicular monoamine transporter type I, norepinephrine transporter, and NPY involved in key processes of catecholamine metabolism in comparison to those with hypertensive pheochromocytomas. This process of downregulation of genes leads to smaller amounts of catecholamines being secreted and thereby presenting with minimal clinical symptoms (16, 17). Patients with non-functioning pheochromocytomas are also known to have a lower prevalence of diabetes suggesting a lower level of catecholamine synthesis compared with those with functioning tumours.

The patients need to be properly prepared before surgery, a multidisciplinary is necessary to guarantee the best possible outcome. As of today, improved preoperative medical preparation

and modern anaesthesia along with surgical techniques have resulted in a very low perioperative mortality of less than one percent (18). Medical preparation is necessary to prevent dangerous complications due to massive surges of catecholamine release. A preoperative evaluation of the cardiovascular system that includes an electrocardiogram, an echocardiography is a must. An effective alpha blockade is necessary in all patients. Calcium channel blockers have been added to alpha-blockers recently. Beta-receptor blockade is part of the treatment to reduce tachycardia and tachyarrhythmia (8). Tumour resection is the standard of care especially when done using minimally invasive procedures. Follow-up of these patients for long-term is necessary.

The patient in our study presented with vague abdominal pain and neither had hypertension nor diabetes mellitus. The abdominal ultrasonography revealed the adrenal mass. The laboratory tests were negative for increased catecholamine secretion. It was histopathology which clinched the diagnosis. Non-functioning pheochromocytomas pose a significant challenge to clinicians and commonly present as adrenal incidentalomas in imaging studies. Pheochromocytomas with normal blood pressure have distinct clinical, biological, and molecular characteristics distinct from pheochromocytomas that present with hypertension. There also appears to be a difference in the concentration of urinary catecholamines between the two types of pheochromocytomas. The use of preoperative  $\alpha$  blockade or the use of calcium channel blockers in non-functioning pheochromocytomas is debatable but may help manage hemodynamic instability. However, the long-term outcome of non-clinical/functioning pheochromocytomas needs further evaluation.

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