Introduction

Adrenal incidentalomas (AI) constitute almost 2% of all the abdominal CT scan findings, out of which almost 5% of lesions constitute Pheochromocytomas (PC) [1]. Given the rarity of PCs in general, almost 10–15% of all PCs are estimated to be silent lesions irrespective of their biochemical picture, thus making it potentially difficult to diagnose and a life-threatening entity [2, 3]. Alarming is that several autopsy studies have suggested the postmortem prevalence of PCs to be as high as 43%, emphasizing the need to routinely measure fractionated plasma or 24 hr urinary metanephrines in all cases of AI to exclude occult and asymptomatic PCs [4, 5]. Recent trends suggest an increase in the incidence of incidentally discovered PCs from 10% to a range of 20–64% of all the pheochromocytomas that are diagnosed [6, 7]. Amongst the incidentally discovered PC cases, absence of hypertension has been reported in almost 25–55% [6, 8–10] cases in various series. Generally, 90% of the patients with PC have either sustained or paroxysmal hypertension, while the classical triad of headache, excessive truncal sweating, and palpitation is encountered in only 10% of all the patients [9]. Normotension with minimal or absent clinical findings are mostly found in small sized PCs or in larger tumors with extensive intratumoral hemorrhage and necrosis, it is also
found in dopamine secreting tumors or amongst patients with familial PCs, or in PCs with succinate dehydrogenase subunit-B (SDHB) mutations [11]. Amongst pheochromocytoma patients sustained hypertension is seen in almost half, episodic hypertension in a third and the normotensive form in less than a fifth of the patients. Normotensive Incidental Pheochromocytomas (NIP) often presents to us as a histological surprise and are rarely reported with fewer mentions in the available literature. Demonstration of elevated circulating catecholamines have always been a key diagnostic feature for identifying PCs in general but these biochemical tests have lower positive predictive values along with suboptimal specificity, besides being less sensitive in cases of NIP [3]. Owing to their diagnostic challenge it is always prudent to plan surgery for suspicious lesions regardless of their symptoms keeping NIP in the back of our mind.

Case report

We report a case of a 41-year-old gentleman, non-hypertensive and non-diabetic, coming from a remote village, who was admitted to our hospital with a provisional diagnosis of an adrenal incidentaloma. He had a 6-month-old abdominal ultra-sonogram report which stated a 47 × 36 mm left suprarenal region mass. Except having complaints of a vague upper abdominal pain since last 1 year he gave no history suggestive of headaches, palpitations, excessive sweating or recent changes in weight. There was no family history of neurofibromatosis or any thyroid, parathyroid, kidney or other abdominal tumors. On examination he had an average built and nutritional status, with no cushingoid features or any dermatological abnormalities. His Eastern Cooperative Oncology Group (ECOG) score was ‘0’ and BMI was 19.72 kg/m². In supine position and upon standing for 2 minutes his baseline pulse rate and blood pressure (BP) were 76 beats/min and 132/80 mm Hg, and 90 beats/min and 126/76 mm Hg respectively. There were no ophthalmological abnormalities or neck lumps, abnormal chest or abdominal findings. Intensive BP monitoring did not reveal any paroxysmal hypertensive peaks.

Going forward with the diagnosis of an adrenal incidentaloma, we ordered a contrast CT scan of abdomen and thorax followed by a plasma free metanephrine level of 19.72 μg/L and 0 μg/L respectively. There were no ophthalmo-logic abnormalities or neck lumps, abnormal chest or abdominal findings. Intensive BP monitoring did not reveal any paroxysmal hypertensive peaks.

200 mm systolic for a brief period of time and came down to normal levels once the vessels were ligated and specimen delivered. He had an uneventful post-operative course and was discharged on the 4th post-operative day. His histopathology revealed a 55 × 50 × 20 mm grayish encapsulated mass which weighed 42 g with absorbed formalin (Fig. 2). Cross-section revealed solid and cystic areas with hemorrhagic foci. Studied sections were consistent with a classical benign PC (Fig. 3). IHC was strongly positive for Neuron specific Enolase (NSE) (in cytoplasm of most of the tumoral cells) and chromogranin A. At 12 months in his follow-up visit patient was healthy and doing well. His plasma metanephrine levels and abdominal USG were within normal limits.

Discussion

Pheochromocytoma is a rare catecholamine releasing neuroendocrine tumor arising from chromaffin cells of the adrenal medulla, the estimated worldwide incidence rates are about 2–8 per million persons per year while the lesion is prevalent in about 0.1 % of all the hypertensive patients [9]. Most of these tumors remain undiagnosed throughout lifetime as it is evident from several postmortem prevalence studies. The most plausible reason behind this may be the fact that none of the described signs and symptoms either alone or when grouped are sensitive or specific enough to give a concrete clinical diagnosis [8, 12].

In clinical practice management of an AI essentially deals with firstly determining its functionality and then ruling out evidence of malignancy. For diagnosis, initial biochemical testing by plasma free metanephrines has a high sensitivity of 96 % and a specificity of 85 % [13]. In comparison, a 24-hour urinary level of catecholamines and metanephrines has a sensitivity of 87.5 % and a specificity of 99.7 % [14], but it is less sensitive for diagnosing a normotensive PC than a hypertensive PC [15, 16]. Based on AACE/AAES/NANETS guidelines and our institutional protocol for AI, we went ahead with a plasma free metanephrine, serum cortisol and other hormonal assays to evaluate the lesion [4] [table 1]. Our patient was normotensive, had no clinical features of catecholamine or glucocorticoid excess and his plasma free metanephrine and urinary VMA levels were normal. Contrast CT features were suggestive of a 5.3 cm sized encapsulated adrenal mass (22 HU on NCCT) with no other mass lesions in the thorax or abdomen. We had very little reason to suspect a case of PC. For a suspected pheochromocytoma, we may perform a metabolic scan viz. 123 or 131 I-MIBG or 68Ga-DOTATATE, however, if the lesion is well visualized and enhancing on CT and no other mass lesion noted anywhere in the thorax or abdomen, a metabolic scan may not be prescribed [17, 18]. CT attenuation by HU, contrast enhancement, contrast washout and margins are the most important radiological diagnostic tools to differentiate AIs. The mean attenuation values of less than 10 HU on unenhanced CT are fairly specific for differentiating adenomas from non-adenomas. An absolute washout value of less than 50 % is highly specific for adenomas [19–22]. Lipid content of malignant tumors are usually low and they generally have attenuation values higher than 20 HU. Irregular borders, heterogeneous consistency, dense contrast enhancement, invasion into the surround-
ing tissues, and metastatic retroperitoneal lymph nodes are important pointers for determination of malignancy. PCs are often well-defined masses with attenuation values similar to those of muscle tissue, measuring approximately 30–40 HU [21]. These must be put in the perspective of existing clinical features along with elicitation of any documented history of malignancy or endocrine disease along with a detailed family and genetic history to arrive at a plausible diagnosis.

Normotensive Incidental Pheochromocytoma (NIP) has different biochemical, cellular and molecular characteristics as described by M. Haissaguerre et al. [15]. According to their study, there was no difference between NIP and Hypertensive Pheochromocytoma (HP) groups in terms of age, sex ratio, tumor size and prevalence of positive uptake on MIBG-scin-tigraphy. However, urinary free catecholamines (sum of free dopamine, noradrenaline, and adrenaline) were significantly lower in patients with NIPs than in those with HPs. The NIP group exhibited a biochemical phenotype different from that of the HP group, characterized by a global reduction in catecholamines and metanephrine secretion, more specifically, secretion of adrenaline and metadrenaline, which in turn can also be corroborated by the fact that there is a lower prevalence of diabetes in patients with NIP due to reduced secretion of catecholamines [23]. The mean PASS (Pheochromocytoma of adrenal gland Scale Score) was also found to be increased in the NIP group compared with that in the HP group contrary to our finding. Also, the NIP group exhibited increased cellularity and number of mitoses and displayed atypical mitosis compared with those in the HP group [15]. The amount and pattern of the catecholamines secreted usually account for hemodynamic features of patients with PCs, low circulating catecholamines and intermittent release are associated with weak clinical expression.

Rarely non-secreting or non-functional abdominal PC/Paragangliomas may present as NIPs either due to lack of catecholamine synthesis or associated to succinate dehydrogenase (SDHB) mutations. Metabolisation of catecholamines to inactive compounds or presence of defective tyrosine hydroxylase enzyme activity may be the possible mechanisms for these lesions being non secretory. In the literature, only rarely the lack of catecholamine release and its causes have been convincingly documented [24]. These tumors are clinically silent and incidentally discovered at radiology or at autopsy or, when they turn out to be malignant, manifesting as metastatic disease.

The incidental pheochromocytoma cases that are smaller than 1 cm generally have no clinical symptoms [25] and it is only on rare occasions, such as ours that a large pheochromocytoma does not show any clinical symptom [26]. It is also estimated that as much as over 50% of the MEN2A associated PCs are found to be asymptomatic at the time of diagnosis [27]. PC is closely related to MEN(2A) syndrome with incidences ranging up to 50% [26] hence it is advisable to screen for components of this syndrome whenever faced with a suspicious lesion with atypical presentation.

Preoperative management of hypertensive PC with α1-adrenoceptor blockade is useful in preventing catecholamine-induced complications during the perioperative period, such as hypertensive crisis, arrhythmias, and pulmonary edema [28, 29]. However, the efficacy and necessity of preoperative management with α-adrenoceptor blockade in NIP patients is controversial [30–32] in retrospective almost justifying our step of avoiding usage of preoperative alpha blockade. Nonetheless, it is always advisable to keep an open mind and prime our anesthetists and intensivists whenever encountered with a suspicious lesion.

Although laparoscopic adrenalectomy is presently recommended for adrenal masses < 8 cm in size, we opted for the left subcostal open approach after discussing with the patient and anesthesia team [33, 34]. In cases of catecho-lamine secreting Pheochromocytoma, few patients suffer from hypotension in the immediate post operative period, which is best remedied by administration of fluids. Post-operative hypoglycemia is transient, whereas low blood pressure and orthostatic hypotension may persist for up to a

![Figure 1. Encapsulated 53 x 41 mm mass in the left suprarenal region (CT-abdomen)](image1.png)

![Figure 2. 55 x 50 x 20 mm grayish encapsulated mass which weighed 42 g (histopathology)](image2.png)
day or more after surgery and require care with assumption of sitting or upright posture [35]. For us the histopathological diagnosis from the final specimen along with the immunochemical staining for specific neuroendocrine markers clinched the final tissue diagnosis of PC. This was of utmost importance to this case as there was no biochemical evidence or metabolic scan to point us towards the diagnosis of a pheochromocytoma pre-operatively.

The long-term prognosis of patients after resection of normotensive PC remains uncertain. Biochemical testing should be repeated after about 14–28 days from surgery to check for remnant disease. Importantly, normal postoperative biochemical test results do not exclude remaining microscopic disease so that patients should not be misinformed that they are cured and that no further follow-up is necessary. In general, PCs are malignant in approximately 10% of patients; recurrence or malignant behavior of PCs occurs more often in patients with large adrenal tumors (>5 cm), extra-adrenal disease, a familial (hereditary) form, or SDHB gene mutations than in those with small adrenal tumors or a sporadic form [36]. Histological differentiation between benign and malignant tumors is difficult; the latter is diagnosed by the presence of metastatic disease or recurrence, whereas a high PASS, as a postoperative histological marker, may be predictive of recurrence [37, 38].

Conclusions

In the absence of hypertension and other classical clinical features of pheochromocytoma coupled with a normal plasma metanephrine level, it was a sort of histological surprise for us that the lesion turned out to be a PC. Although we did preload the patient with intravenous fluids 36 hrs prior to the surgery but intraoperatively the transient increase in blood pressure while handling the tumor hinted us towards the possibility of a PC. The rarity of a truly non-functioning adrenal pheochromocytoma is such that one can only learn from the few reported cases worldwide and approach it as one would in an adrenal incidentaloma. From our experience we would re-iterate the importance of anticipating the possibility of a PC in all enhancing lesions of adrenal gland irrespective of the symptoms and thoroughly investigate keeping in mind the possibility of a NIP.

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Феохромоцитома без артериальной гипертензии: редкий клинический случай

Резюме. Феохромоцитома — довольно редкая нейроэндокринная пухлина, которая секретирует в кровоток высококоактивные адренергические нейромедиаторы — катехоламины. При этом не все випадки феохромоцитом демонстрируют ясную симптоматику. У клинической практики иногда тяготят приходящие и атипичные формы, нормотензивная (с нормальным уровнем метанефрине в плазме для авторов) феохромоцитома демонстрирует ясную симптоматику. У клинической практики иноді трапляються приховані й атипові форми, нормотензивна феохромоцитома демонструють яскраву симптоматику. У клінічній практиці іноді трапляються приховані й атипичні форми, нормотензивна феохромоцитома демонструє яскраву симптоматику. У клінічній практиці іноді трапляються приховані й атипичні форми, нормотензивна феохромоцитома демонструє яскраву симптоматику. У клінічній практиці іноді трапляються приховані й атипичні форми, нормотензивна феохромоцитома демонструє яскраву симптоматику. У клінічній практиці іноді трапляються приховані й атипичні форми, нормотензивна феохромоцитома демонструє яскраву симптоматику.

Интенсивный мониторинг АТ не виявил пиков пароксизмальной гипертензии. За исключением артериальной гипертензии и других классических клинических особенностей феохромоцитом в поединке с нормальным ревизией метанефрину в плазме для авторов было несподвижно, что утверждение при гистологическом дослідженні виявилося феохромоцитомою Лишь тимчасовое підвищення АТ під час операції виявлення пухлини вказувало на можливість феохромоцитоми. Феохромоцитома без артериальной гипертензии:

Ключевые слова: феохромоцитома; нормотензивная феохромоцитома; инциденталома надпочечников; «молчаливая» феохромоцитома; безсимптомная феохромоцитома.