Disease and Diagnosis

Dis Diagn. 2023; 12(2):101-105

doi 10.34172/ddj.2023.392

Case Report

Adrenal Incidentaloma With the Diagnosis of Normotensive Pheochromocytoma: A Case Report

Ali AtashAbParvar[1], Feysal Yousefzade[2], Somayeh Kheirandish[1], Sepehr Rasekhi[2], Ghazal Zoghi[3], Masoumeh Kheirandish[1]*

[1]Endocrinology and Metabolism Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
[2]Student Research Committee, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
[3]Cardiovascular Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

***Correspondence to**
Masoumeh Kheirandish,
Email: kheirandishm@yahoo.com

Abstract

Background: Pheochromocytomas (PCCs) are catecholamine-producing neuroendocrine tumors that originate from the adrenal medulla. Their clinical presentations most commonly include hypertension, headache, palpitations, and sweating; however, PCCs are sometimes normotensive and clinically silent.

Case Presentation: A female patient with abdominal pain as well as persistent and crushing left flank pain for the past six months was examined. The imaging studies revealed a mass in the upper pole of the left kidney indicative of a potential adrenal gland tumor; however, she had normal blood pressure (BP). Histopathologic examination of the mass from exploratory laparotomy showed that it was a PCC. Findings from sonography and computed tomography (CT) scan of the left adrenal tumor, along with elevated urinary normetanephrine level and positive iodine-123 metaiodobenzylguanidine (MIBG) scan led to preoperative diagnosis of PCC in our case.

Conclusion: This study highlighted the importance of imaging and biochemical testing in diagnosing PCCs in patients with adrenal incidentalomas (AIs), even though they were normotensive and entirely asymptomatic.

Keywords: Pheochromocytoma, Incidentaloma, Normotensive

Received: January 9, 2022, Accepted: February 8, 2022, ePublished: April 1, 2023

Introduction

Adrenal incidentalomas (AIs) are asymptomatic adrenal masses accidentally found by abdominal imaging. The imaging study is usually performed to evaluate symptoms unrelated to adrenal such as abdominal or back pain and kidney stones (1). In most cases, AIs are nonfunctioning adrenocortical adenomas, but they may require therapeutic interventions in some cases, including hormone-producing adenoma, adrenocortical carcinoma, extra-adrenal tumor metastasis, and pheochromocytoma (PCC) (2).

PCCs account for 5%-25% of AIs reported in previous PCC case series. (3). Hence, they are rare neuroendocrine tumors that originate from adrenal medulla chromaffin cells (4). Most PCCs are active endocrine tumors secreting excess catecholamines whose metabolites are responsible for clinical signs and symptoms, including hypertension (most common), headache, palpitation, and sweating (5-7). However, it has been reported that 5%-15% of all PCCs are normotensive (8). Several functional levels have been suggested for normotensive incidental pheochromocytomas (NIPs). First, the tumor is nonfunctional as it does not secrete catecholamines. Second, the tumor secretes a minimal quantity of catecholamines. Third, most of the catecholamines are inactivated in the tumor and then are released in an inactive form. And finally, there is an increased tolerance of tissue receptors to circulating catecholamines (9). It has been also estimated that the lower level and intermittent release of circulating catecholamines could cause normotensive presentations (10).

The diagnosis of PCCs crucially depends on biochemical tests that measure the levels of catecholamines (epinephrine, norepinephrine) and their metabolites (e.g., metanephrine, normetanephrine) in either urine or blood. After confirmation of the diagnosis, imaging studies are required to localize the tumor (11). PCCs could be life-threatening, especially their cardiac and cerebrovascular complications; however, the tumor is curable if it is diagnosed early and removed with appropriate preoperative management (12). Although the increased urinary excretion of catecholamines and their metabolites is a useful biochemical diagnostic tool for hypertensive PCCs (11), it is less sensitive in normotensive PCC patients regardless of tumor size (13,14), posing a challenge to diagnosing normotensive

PCCs. This study aimed to report a patient who presented with AI and was finally diagnosed with NIP.

Case Presentation

A 56-year-old female patient presented in August 2014 with the complaint of abdominal pain as well as persistent and crushing left flank pain for the past six months. She had no headache, palpitation, sweating, nausea, vomiting, weight loss, or fatigue. The history of her illness showed that she had been admitted to the cardiology department of Shahid Mohammadi hospital, Bandar Abbas, in March 2014 for acute coronary syndrome (ACS). On admission, the physical examination revealed blood pressure (BP): 130/80 mm Hg, heart rate (HR): 90 bpm, respiratory rate (RR): 14/min, and an oral temperature of 37.2ºC. Then she was scheduled for echocardiography in accordance with her history of ACS; however, no remarkable findings were detected. Thus, abdominal sonography was obtained, which revealed two cystic lesions (6 mm and 31 mm in diameter) in the right lobe of the liver as well as a hypoechoic mass 47 mm in diameter in the upper pole of the left kidney. The computed tomography (CT) scan showed two cystic lesions as simple cysts in the right lobe of the liver and a heterogeneous mass in the left adrenal gland (Figure 1).

Since urine biomedical evaluation for AIs was time-consuming, other differential diagnoses of adrenal masses were evaluated. Chest CT scan, bilateral mammography, colonoscopy, and endoscopy were found to be normal. Taking these findings into account, the most commonly related malignancies and metastases were excluded. Urine biochemical investigations (i.e., 24-hour urine) only showed the abnormally high normetanephrine in our patient and, therefore, the diagnosis of PCC was confirmed. The rest of the evaluations were normal. Complete laboratory tests of plasma and urine are shown in Table 1.

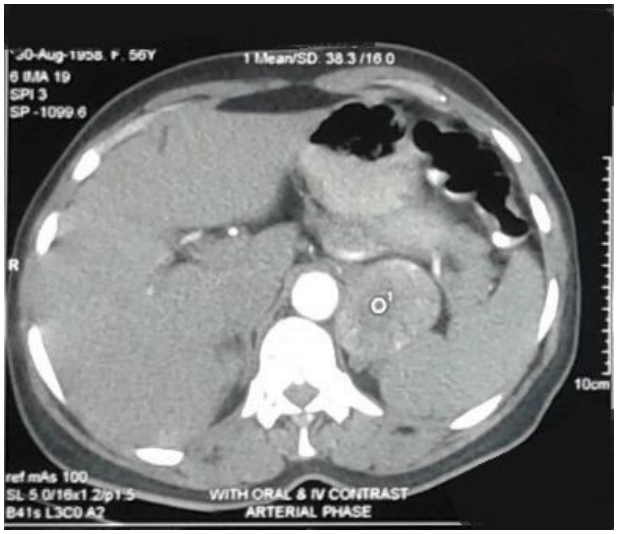

Figure 1. A Large Heterogeneous Mass Lesion (Hyperdense) With Central Necrosis (Hypodense) in Left Adrenal Gland

Then metaiodobenzylguanidine (MIBG) scan was performed as a complementary investigation due to the tumor size (Figure 2A). It increased the probability of PCC (Figure 2), and the patient was consequently transferred to the surgical department.

Intravascular fluid and alfa blockers were administered to the patient before surgery in order to sustain the intravascular volume as well as prevent intraoperative BP rising. An exploratory laparotomy was performed and a left adrenal mass measuring 5×6 cm was resected. The patient experienced an intraoperative hypertension crisis; however, it was appropriately controlled as soon as the tumor was removed. The tumor was well-encapsulated, and the tissue biopsy and histopathological examinations confirmed the diagnosis of PCC. The histopathologic exam is shown in Figure 2B.

The post-surgery clinical progress was good three days after surgery. The patient was transferred to the endocrinology ward for subsequent observation and management, and she was discharged four days later. The urinary normetanephrine value decreased to the normal level two weeks after surgery and remained normal during follow-up.

Discussion

In this study, a clinical case of a 56-year-old woman was examined and, incidentally, diagnosed with normotensive PCC after performing sonography and CT scan.

The most common symptom of PCCs is hypertension and, according to previous studies, it occurs in about

Table 1. Laboratory Values of Plasma and Urine 24 Hours

Laboratory Tests	Results	Reference value
Serum Parameter		
Urea	48 mg/dL	11-55
BUN	22 mg/dL	5-25
Creatinine	0.8 mg/dL	0.5-1.4
Calcium	9.4 mg/dL	8.3-10.8
Sodium	146 mEq/L	132-145
Potassium	4.9 mEq/L	3.5-5.5
Morning cortisol	31.84 ug/dL	6.2-19.4
ACTH	1.6 pg/mL	4.7-48.8
DHEA-SO4	50 µg/dL	26 -200
24-Hour Urine Test		
Metanephrine	33 ug/24 h	Up to 350
Normetanephrine	1948 ug/24 h	Up to 600
VMA	9.7 mg/24 h	Up to 13.6
Urine free cortisol	60 µg/24 h	Up to 120
Urea	13 g/24 h	26-43
Creatinine	888 mg/24 h	600-1800
Urine volume	2400 mLl/24 h	600-1600

Abbreviations: BUN, blood urea nitrogen; ACTH, adrenocorticotropic hormone; DHEA-SO4, dehydroepiandrosterone sulfate; VMA, vanillylmandelic acid.

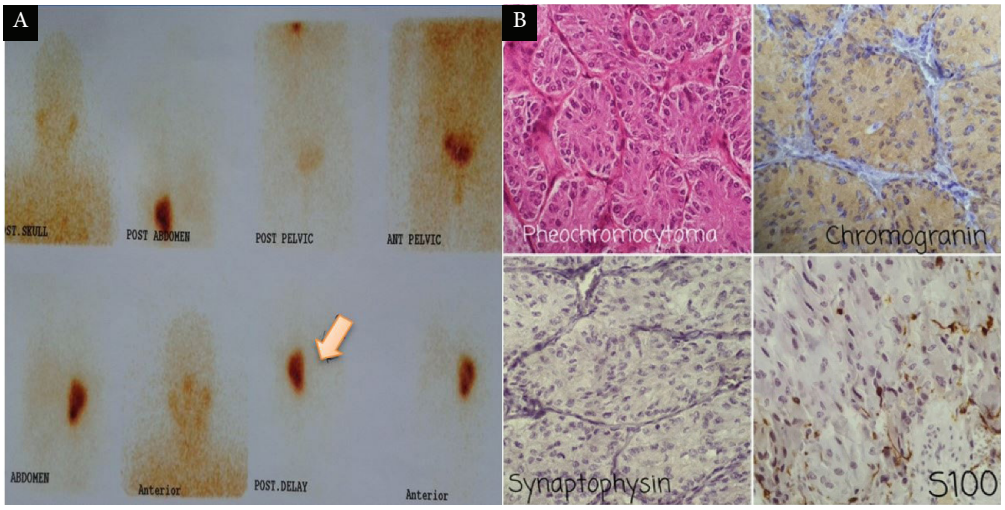

Figure 2. (A) Scan revealed a large area of MIBG uptake at the expected location of left adrenal gland. (B) Zellballen nests of neoplastic cells (hematoxylin and eosin stain), chromogranin- positive cytoplasm of tumor cells (immunohistochemistry [IHC] stain) weak and scattered synaptophysin-positive cytoplasm of tumor cells (IHC stain), and S-100-positive sustentacular cells (IHC stain)

80%-90% of the patients with PCC (6, 15); however, normal BP is expected in 5-15% of patients with PCC (8). Absence of hypertension or hemodynamic manifestations are reported in 10% to 40% of incidental PCC cases (13). The amount and pattern of catecholamines secretion are the factors responsible for hemodynamic features such as high BP in patients with PCC (16,17). The pattern of catecholamine secretion can be continuous, episodic, or both (18). There is some evidence suggesting that low levels of circulating catecholamines and intermittent release are associated with weak clinical presentations like the ones observed in normotensive PCC (10). Although several studies have shown the differences between normotensive and hypertensive PCCs in terms of clinical, hormonal, radiological, and pathological aspects, the molecular mechanisms responsible for such variations have not been investigated yet (13,14).

The index case had neither sustained nor paroxysmal hypertension and had no classic symptoms of PCC, such as headache, palpitation, or weight loss; however, she had high urinary levels of normetanephrine (1948 ug/24 hours) and a positive iodine-123 MIBG scan. She underwent adrenalectomy, and the histopathological analysis of the tumor revealed PCC.

Up to 40% of PCC cases undergo disease-specific germline mutations and are classified as common hereditary tumors. On the other hand, at least one third of the remaining 60% sporadic cases undergoes a somatic mutation in predisposing genes; therefore, it can be stated that about 60% of patients with PCC acquire germline or somatic mutation. To date, more than 20 associated gene mutations have been identified (19-21). Hereditary forms of PCC is associated with genetic syndromes such as multiple endocrine neoplasia type 2, neurofibromatosis type 1, and von Hippel-Lindau syndrome (VHL) (22). Li et al indicated that the patients with VHL were normotensive and had small and multifocal normetanephrine-secreting tumors (23); therefore, it was highly recommended that genetic syndromes in individuals with normotensive PCC be explored.

PCC is associated with various cardiovascular complications, including electrocardiographic changes, arrhythmias, ACS, dilated cardiomyopathy, myocarditis, takotsubo syndrome, and thromboembolism (12). Our patient's history of ACS dated back to 5 months before the visit, while her symptoms, including abdominal and flank pain, had started about 6 months before presentation, suggesting that the patient's heart attack might have been related to PCC.

The diagnosis of PCC is based on detecting an increase in catecholamines levels by biochemical testing as well as on locating the site of the tumor by imaging. Elevated plasma as well as urinary levels of catecholamines and their metabolites, specially metanephrine, indicate the presence of PCC (11); nonetheless, studies have shown that urinary metanephrine is not sensitive enough for diagnosing normotensive PCC (13,14). This has turned the diagnosis of normotensive PCC into a real challenge, emphasizing the role of imaging tools in diagnosing normotensive PCC. PCC diagnostic imaging includes CT scanning, magnetic resonance imaging, meta-MIBG scintigraphy, and positron emission tomography (11). In case when a greater availability of imaging tools has been ensured, the detection rate of incidental normotensive PCCs has increased (24,25). According to the documented findings from CT scan and autopsy series, AIs are common with a prevalence of 2%-5% in the general population. The widespread use of cross-sectional imaging has also increased the recognized prevalence; PCC accounts for 5%-10% of AIs (3).

The choice of treatment for PCC is a complete tumor removal procedure by performing a partial or total

adrenalectomy. Minimally invasive surgical procedures (laparoscopy or retroperitoneoscopy) are the standard approaches in PCC surgery. It is worth of noting that there is limited information about this tumor due to the rate of silent presentation. There are no differences in hemodynamic instability related to the presence or absence of preoperative use of antihypertensives (26).

Preoperative preparation is needed due to using alpha blockers that inhibit catecholamines' effects during the surgery (11). However, Shao and et al found no benefit in using alpha blockers for patients with normotensive PCC; instead, they appear to benefit from colloid infusion and vasoactive drugs. This approach may help prevent hypotension, but it is associated with an increased risk of intraoperative hypertension (27). The two main postoperative complications are hypotension (in 30% of patients) and hypoglycemia (in 15% of patients) due to a considerable decrease in circulating catecholamines after tumor removal. Treatment of these conditions consists of fluid replacement, intravenous ephedrine, and vasopressin administration (28).

The long-term prognosis of patients with normotensive PCC after surgery has remained uncertain. In general, PCCs are malignant in approximately 10% of patients. Recurrence or malignant behavior occurs more often in patients with large adrenal tumors (> 5 cm), extra-adrenal disease, and hereditary form or SDHB gene mutations compared to those with small adrenal tumors or sporadic form. Given the above discussion, a regular follow-up is needed during the patient's lifetime (1).

Conclusion

In this study, a case of incidental normotensive PCC was investigated. A combination of sonography and CT scan findings of the left adrenal tumor, along with elevated urinary normetanephrine level and positive iodine-123 MIBG scan led to preoperative diagnosis of PCC in our case. This report emphasized the importance of imaging and biochemical testing for PCCs in patients with AIs, even when they were normotensive and completely asymptomatic.

Acknowledgments

We wish to sincerely thank our patient for allowing us to share her unique clinical presentation. We would also like to express our gratitude towards the late Dr. Abbas Rahimi who significantly contributed to this article.

Author's Contribution

Drafting of the manuscript: Ali AtashAbParvar and Feysal Yousefzade. Acquisition of data: Somayeh Kheirandish and Sepehr Rasekhi. Critical revision of the manuscript: Ghazal Zoghi. Study supervision: Masoumeh Kheirandish. All authors read and approved the final manuscript.

Availability of Supporting Data

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

Ethical Approval

This study was approved by the Ethical Committee of Hormozgan University of Medical Sciences under the ethics code IR: HUMS. REC.1399.432, and was performed in accordance with the Declaration of Helsinki.

Funding

This research received no specific grant from public funding agencies, commercial, or not-for-profit sectors.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

References

1. Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, et al. Management of adrenal incidentalomas: European society of endocrinology clinical practice guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016;175(2):G1-G34. doi: 10.1530/eje-16-0467.
2. Ohara N, Kaneko M, Yaguchi Y, Ishiguro H, Ishizaki F, Maruyama R, et al. A case of normotensive incidentally discovered adrenal pheochromocytoma. Clin Case Rep. 2018;6(12):2303-8. doi: 10.1002/ccr3.1772.
3. Arlt W. Disorders of the adrenal cortex. In: Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw Hill; 2018. p. 2730-1.
4. Tevosian SG, Ghayee HK. Pheochromocytomas and Paragangliomas. Endocrinol Metab Clin North Am. 2019;48(4):727-50. doi: 10.1016/j.ecl.2019.08.006.
5. Schreiner F, Beuschlein F. Disease monitoring of patients with pheochromocytoma or paraganglioma by biomarkers and imaging studies. Best Pract Res Clin Endocrinol Metab. 2020;34(2):101347. doi: 10.1016/j.beem.2019.101347.
6. Guerrero MA, Schreinemakers JM, Vriens MR, Suh I, Hwang J, Shen WT, et al. Clinical spectrum of pheochromocytoma. J Am Coll Surg. 2009;209(6):727-32. doi: 10.1016/j.jamcollsurg.2009.09.022.
7. Dahia PL. Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity. Nat Rev Cancer. 2014;14(2):108-19. doi: 10.1038/nrc3648.
8. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(6):1915-42. doi: 10.1210/jc.2014-1498.
9. Feldman JM, Blalock JA, Zern RT, Shelburne JD, Gaede JT, Farrell RE, et al. Deficiency of dopamine-beta-hydroxylase. A new mechanism for normotensive pheochromocytomas. Am J Clin Pathol. 1979;72(2):175-85. doi: 10.1093/ajcp/72.2.175.
10. Zuber SM, Kantorovich V, Pacak K. Hypertension in pheochromocytoma: characteristics and treatment. Endocrinol Metab Clin North Am. 2011;40(2):295-311. doi: 10.1016/j.ecl.2011.02.002.
11. Neumann HP. Pheochromocytoma. In: Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw Hill; 2018. p. 2739-46.
12. Y-Hassan S, Falhammar H. Cardiovascular manifestations and

complications of pheochromocytomas and paragangliomas. J Clin Med. 2020;9(8):2435. doi: 10.3390/jcm9082435.
13. Haissaguerre M, Courel M, Caron P, Denost S, Dubessy C, Gosse P, et al. Normotensive incidentally discovered pheochromocytomas display specific biochemical, cellular, and molecular characteristics. J Clin Endocrinol Metab. 2013;98(11):4346-54. doi: 10.1210/jc.2013-1844.
14. Lu Y, Li P, Gan W, Zhao X, Shen S, Feng W, et al. Clinical and pathological characteristics of hypertensive and normotensive adrenal pheochromocytomas. Exp Clin Endocrinol Diabetes. 2016;124(6):372-9. doi: 10.1055/s-0042-100911.
15. Omura M, Saito J, Yamaguchi K, Kakuta Y, Nishikawa T. Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. Hypertens Res. 2004;27(3):193-202. doi: 10.1291/hypres.27.193.
16. Bravo EL, Tagle R. Pheochromocytoma: state-of-the-art and future prospects. Endocr Rev. 2003;24(4):539-53. doi: 10.1210/er.2002-0013.
17. Zhu Y, He HC, Su TW, Wu YX, Wang WQ, Zhao JP, et al. Selective α1-adrenoceptor antagonist (controlled release tablets) in preoperative management of pheochromocytoma. Endocrine. 2010;38(2):254-9. doi: 10.1007/s12020-010-9381-x.
18. Fung MM, Viveros OH, O'Connor DT. Diseases of the adrenal medulla. Acta Physiol (Oxf). 2008;192(2):325-35. doi: 10.1111/j.1748-1716.2007.01809.x.
19. Favier J, Amar L, Gimenez-Roqueplo AP. Paraganglioma and phaeochromocytoma: from genetics to personalized medicine. Nat Rev Endocrinol. 2015;11(2):101-11. doi: 10.1038/nrendo.2014.188.
20. Jochmanova I, Pacak K. Genomic Landscape of Pheochromocytoma and Paraganglioma. Trends Cancer. 2018;4(1):6-9. doi: 10.1016/j.trecan.2017.11.001.
21. Khatami F, Mohammadamoli M, Tavangar SM. Genetic and epigenetic differences of benign and malignant pheochromocytomas and paragangliomas (PPGLs). Endocr Regul. 2018;52(1):41-54. doi: 10.2478/enr-2018-0006.
22. Aygun N, Uludag M. Pheochromocytoma and paraganglioma: from epidemiology to clinical findings. Sisli Etfal Hastan Tip Bul. 2020;54(2):159-68. doi: 10.14744/semb.2020.18794.
23. Li SR, Nicholson KJ, McCoy KL, Carty SE, Yip L. Clinical and Biochemical Features of pheochromocytoma characteristic of von Hippel-Lindau syndrome. World J Surg. 2020;44(2):570-7. doi: 10.1007/s00268-019-05299-y.
24. Agarwal A, Gupta S, Mishra AK, Singh N, Mishra SK. Normotensive pheochromocytoma: institutional experience. World J Surg. 2005;29(9):1185-8. doi: 10.1007/s00268-005-7839-4.
25. Noshiro T, Shimizu K, Watanabe T, Akama H, Shibukawa S, Miura W, et al. Changes in clinical features and long-term prognosis in patients with pheochromocytoma. Am J Hypertens. 2000;13(1 Pt 1):35-43. doi: 10.1016/s0895-7061(99)00139-9.
26. Özveren B, Ulugöl H, Türkeri L. Normotensive, oversized pheochromocytoma in twin-pregnancy: analysis of therapeutic challenges in a rare case. Case Rep Urol. 2019;2019:7141060. doi: 10.1155/2019/7141060.
27. Shao Y, Chen R, Shen ZJ, Teng Y, Huang P, Rui WB, et al. Preoperative alpha blockade for normotensive pheochromocytoma: is it necessary? J Hypertens. 2011;29(12):2429-32. doi: 10.1097/HJH.0b013e32834d24d9.
28. Prakash P, Ramachandran R, Tandon N, Kumar R. Changes in blood pressure, blood sugar, and quality of life in patients undergoing pheochromocytoma surgery: a prospective cohort study. Indian J Urol. 2019;35(1):34-40. doi: 10.4103/iju.IJU_190_18.