Case Report
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Giant Malignant Pheochromocytoma: A Unique Case Report from Turkey

Dev Malign Feokromositoma Vakası

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Abstract

Catecholamine-secreting tumors are rare neoplasms that occur in less than 0.2% of hypertensive patients. While pheochromocytomas are rare neoplasms in the adrenal gland, giant pheochromocytomas are much less common. In this report, we present the case of a 38-year-old man who had a 29x18x12 cm giant malignant pheochromocytoma. During an examination for hematuria, a large mass was detected incidentally in the right adrenal gland of the patient. This mass was diagnosed as pheochromocytoma and proved to be one of the largest pheochromocytomas reported so far; hence, its notification has been considered significant for the medical and research professionals across the world.

Keywords: Adrenal incidentaloma; pheochromocytoma; hematuria; hypertension, malignant; chromaffin cells

Özet

Katekolamin salgılayan tümörler, hipertansiyonu olan hastaların yüzde 0,2'sinden daha azında görülen nadir neoplazilerdir. Feokromositomalar adrenal bezde görülen nadir neoplazilerken, dev feokromositomalar çok daha nadir görülmektedir. Bu vaka bildiriminde 38 yaşında 29x18x12 cm boyutlarında dev malign feokromositoma tespit edilen bir erkek hasta tanımlanmıştır. Hasta hematüri nedeni ile tetkik edilirken sağ adrenal bezinde insidental olarak kitle tespit edilmiştir. Türkiye'de tanımlanmış en büyük feokromositomalardan biri olarak bildiriminin önemli olabileceği düşünülmüştür.

Anahtar kelimeler: Adrenal insidentalom; feokromositoma; hematüri; hipertansiyon, malign; kromafin hücreler

Introduction

Catecholamine-secreting tumors originating from chromaffin cells are of two types: pheochromocytoma from the adrenal medulla and paraganglioma from the sympathetic ganglia.

Pheochromocytomas are rare neoplasms found in less than about 0.2% of the hypertensive patients (1,2). While classical pheochromocytomas are rare, giant pheochromocytomas are much less common. Although most of such tumors remain benign, about 10% become malignant. Although most cases are sporadic, sometimes they can be associated with multiple endocrine neoplasia type 2 (MEN-2), von Hippel-Lindau (VHL) syndrome, and less often with neurofibromatosis type 1 (NF-1) (3,4). Preoperative diagnosis and therapeutic treatments may be difficult for malignant pheochromocytoma patients. The classic symptoms seen in pheochromocytoma patients include episodic headache, sweating, and tachycardia (1,5). About half of the patients show paroxysmal hypertension; the majority of the remaining patients show pri-

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mary hypertension or normal blood pressure. Most of the pheochromocytoma patients do not display all three classic symptoms simultaneously (6,7). The first step in the diagnosis of pheochromocytoma is the biochemical analysis of urine and plasma fractionated metanephrines and catecholamines.

Radiological evaluation is advised after biochemical confirmation of the diagnosis to locate the tumor. Approximately 15% of all pheochromocytomasare extra-adrenal, but 95% of them are within the abdomen and pelvis (4). In order to diagnose the lesion, computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis is usually performed firstly.

Once pheochromocytoma is diagnosed, patients should be operated after necessary medical preparation. During preoperative preparation, sympathetic control with alpha blockage followed by a beta-adrenergic blockade is required. As pheochromocytoma surgery is highly risky, hemodynamic variables should be closely monitored during the operation (8). The choice of approach includes both laparoscopic and open surgery, depending on tumor characteristics and patient factors.

In this case report, a giant malignant pheochromocytoma sized 29x18x12 cm has been presented.

Case Report

A 38-year-old male patient applied to the emergency service with the complaint of blood in the urine. In the abdominal USG performed for the etiology of hematuria, a mass of 25 cm diameter was detected in the right adrenal region. The patient was admitted to the endocrinology clinic to further investigate; differentiate between benign and malignant adrenal mass, and evaluate the hormonal activity. The following indicators were observed during the physical examination: blood pressure 150/90 mmHg; pulse rate 92 beats/min; temperature 36.5 °C; the respiratory system normal; the cardiac rhythm normal. No additional voice and murmur were observed. In the abdominal examination, a mass with regular contours of 20 cm, palpable with deep seated lesion in the right upper and middle quadrant was detected. The patient's biochemical examinations were normal, but urine and plasma adrenaline, noradrenaline, and normetanephrine levels were found to be high in the tests performed for the hormonal activity of the adrenal gland (Table 1).

The patient was diagnosed with pheochromocytoma, and a Holter monitoring device was inserted into him (the patient) to monitor his 24-hour blood pressure. The fundus examination was performed in terms of organ damage due to hypertension that re-

Table 1. Table showing the patient's hormone evaluation with tests, and reference/standard values.

Test	Patient's value	Reference values
ACTH	54.3 ng/L	6.7-22.6 ng/L
Cortisol	22.2 µg/dL	≤46 µg/dL
Dexamethasone Suppression Test (1 mg)	0.75 µg/dL	
Dehydroepiandrosterone Sulfate	61.3 µg/dL	
Testosterone	3.92 µg/L	1.98-6.79 µg/L
Aldosterone (ALD)	25.36 ng/dL	7-30 ng/dL
Plasma Renin Activity (PRA)	3.68 ng/mL/h	0.98-4,18 ng/mL/h
ALD/PRA	4,08	
Plasma Metanephrine Level	39.66 pg/mL	≤90 pg/mL
Plasma Normetanephrine Level	737.19 pg/mL	≤180 pg/mL
Plasma Adrenaline	183.92 ng/L	≤90 ng/L
Plasma Noradrenaline	734.93 ng/L	≤500 ng/L
Urine Metanephrine	158.95 µg/24 h	50-250 µg/24 h
Urine Normetanephrine	2643.27 µg/24 h	100-500 µg/24 h
Urine Adrenaline	37.76 µg/24 h	0-20 µg/24 h
Urine Noradrenaline	114.77 µg/24 h	15-80 µg/24 h

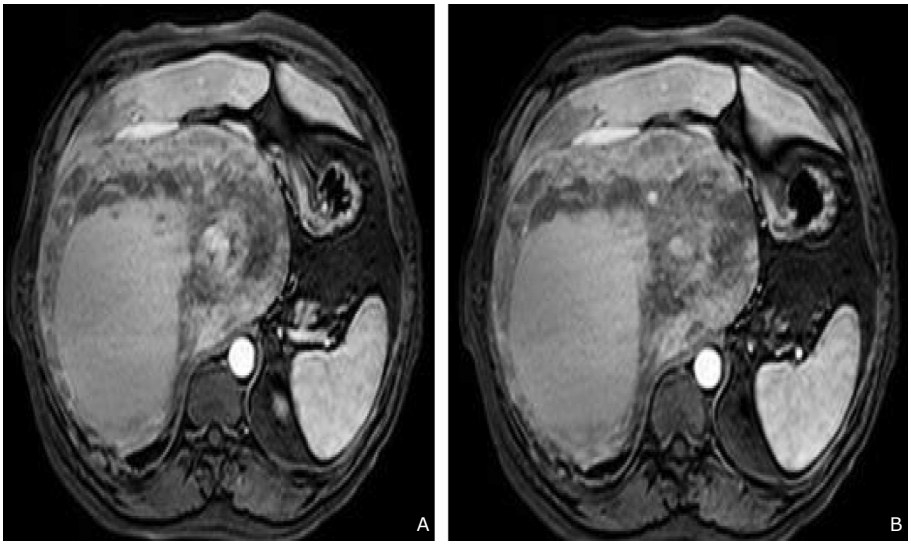

Figure 1. A) Mass lesion in heterogenous enchantment of the right adrenal gland from the superior to the liver, **B)** Inferior to the right boundary-pushing the portal vein anterior-superior, crossing the midline.

vealed stage 1 hypertensive retinopathy. Left ventricular hypertrophy was seen on echocardiography.

In the abdominal MRI, the following features were detected.

There was a mass lesion in the right adrenal gland, 216 x 167 mm in size from the superior to the liver, inferior to the right boundary pushing the portal vein anterior-superior, crossing the midline, solid character with cystic-necrotic areas, and showing heterogeneous enchantment of the adrenal gland (Figure 1A, B).

After the examinations and imaging, the right adrenalectomy was recommended to the patient. In order to prevent a potential hypertensive crisis during the operation, the patient was initiated on alpha blockade with dibenzyran and then with propranolol during the preoperative period and was operated for mass excision in March 2019 by general surgery. No hypertensive attack during the operation was reported. Macroscopic examination of the surgical specimen showed a brown color, a heterogeneous tumoral lesion that measured 29x18x12 cm, weighed 1490 grams with cystic cavities filled with necrotic and bleeding fluids on large areas (Figure 2).

In the immunohistochemical study, chromogranin A(CgA), synaptophysin, and S-100 protein were positively stained. Ki-67 labeling index was reported as 1%.

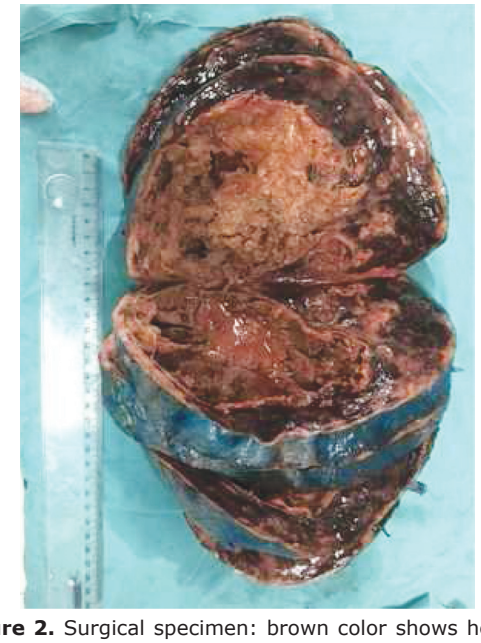

Figure 2. Surgical specimen: brown color shows heterogeneous lesion (size 29x18x12 cm, weight 1490 grams), with the cystic cavity filled with necrotic and bleeding fluids in adjoining areas.

The histopathological result confirmed pheochromocytoma (Figure 3A-C).

As the mass was evaluated as high malignancy potential due to the pheochromocytoma of the Adrenal Gland Scaled Score (PASS) of 11, PET-CT scan was performed to detect any pathological involvement or metastasis focus. The patient showed normal levels of postoperative urine and plasma

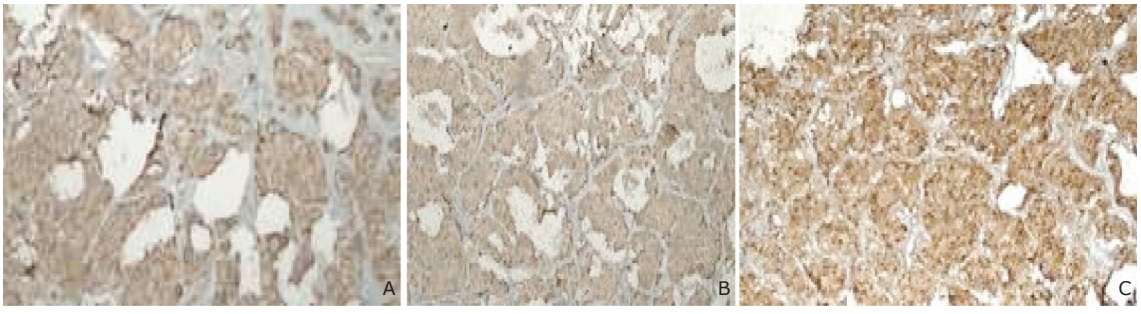

Figure 3. Pheochromocytotoma white lesions seen in an immunohistochemical analysis showing staining of chromogranin A **(A)**, Synaptophysin [**(B)** and S-100 **(C)**].

catecholamines and was followed up as normotensive without using any medication.

Discussion

Pheochromocytomas are rare neoplasms emanating from chromaffin cells of the sympathoadrenal system (9). Eighty-five percent of the pheochromocytomas occur in the adrenal medulla region (10). Pheochromocytomas may generally occur from the fourth to the fifth decade, equally in men and women.

The majority of the pheochromocytomas are benign, and about 10 percent are malignant (5). As the size of the mass increases, the risk of malignancy also increases. Malignancy risk is eight times greater, especially in lesions larger than 6 cm.

The malignant potential of pheochromocytoma cannot be determined preoperatively if there is no prior evidence of metastases. In our case, there was no metastasis focus in all body images. Thompson (11) evaluated 50 benign and 50 malignant pheochromocytomas histopathologically and found histological features such as necrosis, atypia, increased mitosis, nuclear polymorphism, and diffuse growth to be more common in malignant tumors. Each feature was scored and pheochromocytoma profiling by the PASS was done, 4 or more results were evaluated as aggressive biological features. Since the PASS in our case was 11, the malignancy potential was considered high.

Due to the low incidence of malignant pheochromocytomas, there is insufficient data regarding prognosis and survival. Five-year survival is generally below 50% in metastatic pheochromocytomas. These patients should be followed lifelong.

Pheochromocytoma is usually detected by examining asymptomatic patients, detecting an adrenal mass incidentally, or scanning a patient with familial disease. Fifty percent of the patients with pheochromocytoma display some typically paroxysmal symptoms. The classic triad of symptoms includes episodic headache, sweating, and tachycardia (1,6). Interestingly, the patient was asymptomatic with an adrenal mass of about 30 cm. In a study in, which 20 cases of pheochromocytoma greater than 10 cm were presented, 13 patients had abdominal pain while only five had classic symptoms of pheochromocytoma (12). In our case, the patient was diagnosed incidentally while he was being examined due to hematuria.

Surgery is the treatment of choice in patients diagnosed with pheochromocytoma. In the current case, open surgery was preferred due to the large size of the mass. The patient was successfully operated with preoperative preparations. Postoperative urine and plasma catecholamine levels were found to be normal.

The average mass size in pheochromocytomas is approximately 7 cm. In the literature search covering summaries of all giant (>10 cm) pheochromocytomas (13), the largest tumor was reported as 45x20 cm (14). Although, previously rare cases of average size have been reported in Turkey (15), this remarkable case showcases one of the largest pheochromocytomas ever reported in Turkey.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Damla Tüfekçi; Design: Damla Tüfekçi, Yasemin E. Günay; Control/Supervision: Damla Tüfekçi, İrfan Nuhoğlu; Data Collection and/or Processing: Damla Tüfekçi, Yasemin E. Günay, Ahmet Suat Demir; Analysis and/or Interpretation: Damla Tüfekçi, Hülya Coşkun, İrfan Nuhoğlu, Mustafa Koçak; Literature Review: Damla Tüfekçi; Writing the Article: Damla Tüfekçi; Critical Review: Damla Tüfekçi, Yasemin E. Günay, İrfan Nuhoğlu; References and Fundings: Damla Tüfekçi, Mustafa Koçak.

References

1. Stein PP, Black HR. A simplified diagnostic approach to pheochromocytoma. A review of the literature and report of one institution's experience. Medicine (Baltimore). 1991;70:46-66. [Crossref] [PubMed]
2. Pacak K, Linehan WM, Eisenhofer G, Walther MM, Goldstein DS. Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. Ann Intern Med. 2001;134:315-329. [Crossref] [PubMed]
3. Neumann HP, Berger DP, Sigmund G, Blum U, Schmidt D, Parmer RJ, Volk B, Kirste G. Pheochromocytomas, multiple endocrine neoplasia type 2, and von Hippel-Lindau disease. N Engl J Med. 1993;329:1531-1538. [Crossref] [PubMed]
4. Bravo EL. Evolving concepts in the pathophysiology, diagnosis, and treatment of pheochromocytoma. Endocr Rev. 1994;15:356-368. [Crossref] [PubMed]
5. Bravo EL. Pheochromocytoma: new concepts and future trends. Kidney Int. 1991;40:544-556. [Crossref] [PubMed]
6. Kudva YC, Young WF, Thompson GB, Grant CS, Van Heerden JA. Adrenal incidentaloma: an important component of the clinical presentation spectrum of benign sporadic adrenal pheochromocytoma. The Endocrinologist. 1999;9:77-80. [Crossref]
7. Baguet JP, Hammer L, Mazzuco TL, Chabre O, Mallion JM, Sturm N, Chaffanjon P. Circumstances of discovery of phaeochromocytoma: a retrospective study of 41 consecutive patients. Eur J Endocrinol. 2004;150:681-686. [Crossref] [PubMed]
8. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, Naruse M, Pacak K, Young WF Jr; Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99:1915-1942. [Crossref] [PubMed]
9. Pederson LC, Lee JE. Pheochromocytoma. Curr Treat Options Oncol. 2003;4:329-337. [Crossref] [PubMed]
10. Dahia PL. Evolving concepts in pheochromocytoma and paraganglioma. Curr Opin Oncol. 2006;18:1-8. [Crossref] [PubMed]
11. Thompson LD. Pheochromocytoma of the Adrenal gland Scaled Score (PASS) to separate benign from malignant neoplasms: a clinicopathologic and immunophenotypic study of 100 cases. Am J Surg Pathol. 2002;26:551-566. [Crossref] [PubMed]
12. Korgali E, Dundar G, Gokce G, Kilicli F, Elagoz S, Ayan S, Gultekin EY. Giant malignant pheochromocytoma with palpable rib metastases. Case Rep Urol. 2014;2014:354687. [Crossref] [PubMed] [PMC]
13. Maharaj R, Parbhu S, Ramcharan W, Baijoo S, Greaves W, Harnanan D, Warner WA. Giant cystic pheochromocytoma with low risk of malignancy: a case report and literature review. Case Rep Oncol Med. 2017;2017:4638608. [Crossref] [PubMed] [PMC]
14. Grissom JR, Yamase HT, Prosser PR. Giant pheochromocytoma with sarcoidosis. South Med J. 1979;72:1605-1607. [Crossref] [PubMed]
15. Uysal E, Kırdak T, Gürer AO, İkidağ MA. Giant multicystic malignant pheochromocytoma. Turk J Surg. 2015;33:296-298. [Crossref] [PubMed] [PMC]