

ORIGINAL ARTICLES

Pitfalls in the diagnosis of pheochromocytoma: A case series and review of the literature

Mine Adas¹, Bora Koc², Gokhan Adas², Orhan Yalcin², Sebahattin Celik*³, Özgür Kemik³

¹Department of Endocrinology, Okmeydani Training and Research Hospital, Istanbul, Turkey

²Department of Surgery, Okmeydani Training and Research Hospital, Istanbul, Turkey

³Department of Surgery, Faculty of Medicine, Yuzuncu Yil University, Turkey

Received: November 20, 2015

Accepted: January 18, 2016

Online Published: January 31, 2016

DOI: 10.5430/jer.v2n2p49

URL: <http://dx.doi.org/10.5430/jer.v2n2p49>

ABSTRACT

Background: Pheochromocytomas (PC) are neuroendocrine catecholamine-releasing tumors, which arise from chromaffin cells in the adrenal medulla. The clinical presentation of PC depends mostly on the capacity of chromaffin cells to synthesize and release catecholamines, including noradrenaline, adrenaline, dopamine and others. In this case series, we present the pitfalls in the diagnosis and treatment of pheochromocytoma in which the clinical presentation and results of laboratory, radiologic, and nuclear investigations led to an incorrect diagnosis.

Case presentation: From 2002 to 2013, seven patients who were misdiagnosed and had pitfalls during treatment were found among 30 patients with pheochromocytoma. We retrospectively reviewed all the medical records of the patients. The data recorded for these seven patients included general demographic data, medical history, symptoms, imaging and laboratory results, histologic interpretation of biopsy and final pathology, and morbidities or mortalities.

Conclusion: Correct diagnosis and management of pheochromocytoma is clinically important because misdiagnosis leads to high morbidity and mortality secondary to hypertensive crisis. The critical interpretation of each diagnostic test, attentive review of functional examinations, anatomic imaging methods, and careful history taking is essential for a correct diagnosis.

Key Words: Pheochromocytoma, Pitfalls, Misdiagnosis, Incidentaloma

1. INTRODUCTION

Pheochromocytomas (PC) are neuroendocrine catecholamine-releasing tumors, which arise from chromaffin cells in the adrenal medulla.^[1] Approximately 85% of PCs arise in the chromaffin cells of the adrenal medulla; 18% may be extra-adrenal. When PCs develop outside of the adrenal gland, the tumors are referred to as a secreting paragangliomas.^[2,3] This neuroendocrine tumor is a deceptive and treacherous disease because if it is not recognized and treated appropriately, it will almost certainly lead to fatal cardiovascular or cerebrovascular disease or devastating

complications.^[4] PCs occur most frequently in individuals aged 40-50 years, with a slight predilection in females.^[3]

The clinical presentation of PCs depends mostly on the capacity of chromaffin cells to synthesize and release catecholamines, including noradrenaline, adrenaline, dopamine, and others. In patients with classic symptoms, including headache, palpitations, sweats, and sustained or paroxysmal hypertension, the diagnosis is excluded by repeated findings of normal catecholamine production.^[5] Surgeons and anesthesiologists who care for such patients must have an

*Correspondence: Sebahattin Celik; Email: scelik@yyu.edu.tr; Address: Department of General Surgery, Faculty of Medicine, Yuzuncu Yil University, Turkey.

awareness of this condition to provide timely and appropriate management because the management of any surgical patient with PC is challenging.^[6,7] Manipulation of the adrenal gland during biopsy, especially in catecholamine-producing tumors such as pheochromocytoma and paragangliomas, may cause a catecholamine surge, which results in hypertensive crisis. Severe hypertension associated with manipulation of pheochromocytomas can cause cardio-cerebrovascular complications such as myocardial ischemia, arrhythmia, cerebral hemorrhage, or aortic dissection during the perioperative period.^[8]

Although recent advances in diagnostic imaging, pharmacologic treatment, surgical techniques, and molecular profiling have contributed to a better understanding of the disease, it still represents a dilemma for physicians. In this case series, we present the pitfalls in the diagnosis and treatment of

pheochromocytoma in which the clinical presentation and results of laboratory, radiologic, and nuclear investigations led to an incorrect diagnosis. Additionally, we present this case series to emphasize potential clinical misdiagnoses of pheochromocytoma and to prevent their repetition.

2. CASE PRESENTATION

From 2002 to 2013, seven patients who were misdiagnosed and had difficulties during treatment were found among 30 patients with pheochromocytoma. We retrospectively reviewed all the medical records of the patients. The data recorded for these seven patients included general demographic data, medical history, symptoms, imaging and laboratory results, histologic interpretation of biopsy and final pathology, and morbidities or mortalities. The patients' findings are summarized in Table 1.

Table 1. Summary of the patients' characteristics

	Age/sex (years)	Clinical Presentation	CT	MR	PET (SUVmax)	Biopsy (+/-)	Biochemical Findings	Treatment
Case 1	26/F	Abdominal discomfort	Left-sided retroperitoneal mass	Hemorrhagic necrotic mas	7.1	PC	High	Drainage+ catheter placement+ adrenalectomy
Case 2	41/M	Hypertensive crisis during hemorrhoid operation	Left adrenal mass	-	-	-	High	Adrenalectomy
Case 3	69/F	Incidentaloma	-	Hyper-intense mass	7.9	-	Normal	Adrenalectomy
Case 4	54/F	Abdominal pain	Suspicious left kidney mass	-	-	-	-	Drainage (2 times)+ nephrectomy
Case 5	55/F	Breast cancer follow-up	Left adrenal mass	Cystic lesion	3.2	-	Normal	Adrenalectomy
Case 6	50/M	Abdominal pain	Suspicious left kidney mass	-	-	-	-	Nephrectomy
Case 6*		Right knee pain	-	-	4.3	PC met	High	CT+RT
Case 7	32/F	Headache Hypertension	Left adrenal mass	-	-	PC	Normal	Adrenalctomy

Note. PC: Pheochromacytoma, CT: Computerized Tomography, MR: Magnetic Resonance, PET: Positron-emission tomography; SUVmax: Standard uptake value. SUVmax levels showed adrenal up-take, except in case 6; *Second admission with knee metastasis of PC, SUVmax level showed right knee up-take. Biopsy (+/-); biopsy was (+).

2.1 Case 1

A woman aged 26 years was admitted for general surgery because of abdominal discomfort and was diagnosed as having a left-side localized 11 cm × 17 cm × 18 cm retroperitoneal mass with hemorrhagic, cystic necrotic components on an abdominal computerized tomography (CT). On T1A-weighted magnetic resonance (MR) images, the tumor was observed as a slightly hyper-intense mass and had characteristic hemorrhagic necrotic components. The patient was then referred to the interventional radiology department for drainage and biopsy under CT (see Figure 1). A total of 1,800 cc of liquid was aspirated, and thrombolytic treatment was performed on the cystic tumor. A tru-cut biopsy was taken. After this procedure, the patient's blood level decreased due to bleeding. While the patient was in the surgical department, a ¹⁸F-2-Fluoro-deoxy-D-glucose-positron emission tomogra-

phy scan was performed, which showed a standard uptake value (SUVmax) of 7.1 of the left 11 cm × 18 cm × 17 cm adrenal mass. The result of the tru-cut biopsy showed a chromogranin (+), vimentin (+), and CK (-) pheochromocytoma. After this result, the patient was referred to the endocrinology department for biochemical evaluation and prepared for surgery. A left adrenalectomy was performed, and the patient was discharged without any complications. The final diagnosis was found to be pheochromocytoma, and the histopathologic features were chromogranin (+), synaptophysin (+), S-100 (+), vimentin (+), EMA (-), CK7 (-), and Inhibin (-).

2.2 Case 2

During a hemorrhoid operation, a man aged 41 years had a hypertensive crisis. The The patient was evaluated because

of hypertensive crisis and was found to have a 40 mm × 50 mm left adrenal mass, which lead to a presumptive diagnosis of pheochromocytoma. Twenty-four hour urinary catecholamines were measured and were found to be elevated. A complete resection of the tumor was performed, and the final pathology reported pheochromocytoma.

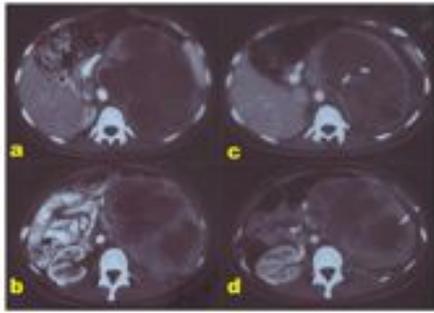


Figure 1. a-b: A left-side localized 11 cm × 17 cm × 18 cm retroperitoneal mass with hemorrhagic, cystic necrotic components on an abdominal computerized tomography; c-d: placement of a drainage catheter inside a PC

2.3 Case 3

A woman aged 69 years was diagnosed as having a 2.5 cm right adrenal incidentaloma. Biochemical tests to determine the functional hormone secretion were within the normal range. The tumor was observed as a slightly hyper-intense mass on T1A-weighted MR images. After intravenous injection of gadolinium, the mass showed progressive, heterogeneous, and delayed enhancement that confirmed that it was not adenoma. Positron-emission tomography-computerized tomography (PET-CT) showed an SUVmax of 7.9, which confirmed malignancy. The patient was consequently transferred for surgical intervention. After an uneventful surgical resection, the mass was revealed as pheochromocytoma.

2.4 Case 4

A woman aged 54 years was diagnosed as having a 14-cm left kidney cyst, which had been aspirated under CT in the radiology department twice within nine months. Afterwards, the patient was referred to the urology department and an exploratory laparotomy with tumor resection was scheduled. During the operation, the patient's blood pressure abruptly surged to 250/170 mmHg, with fluctuations. After her vital signs were brought under control, the tumor was removed. The pathologic report confirmed a diagnosis of pheochromocytoma.

2.5 Case 5

A woman aged 55 years with a known history of breast cancer was diagnosed as having a 3-cm left adrenal mass that

consisted of metastases with an SUVmax of 3.2 at PET-CT. Magnetic resonance imaging confirmed a 27 mm × 23 mm well-encapsulated cystic lesion; on T1A-weighted MR images, the tumor was seen as a slightly hypo-intense mass, but on T2A-weighted MRI the tumor was a distinct hyper-intense mass. The patient was considered to have a metastasis of breast cancer, and a right adrenalectomy was performed. The pathologic diagnosis was confirmed to be pheochromocytoma.

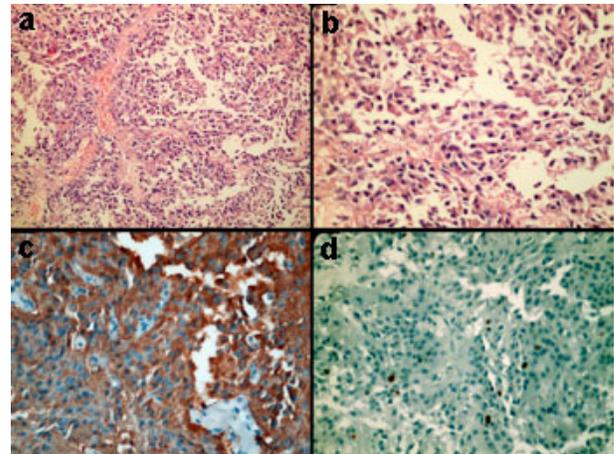


Figure 2. a-b: The tumors are composed of intermediate to large polygonal cells that may be arranged in alveolar, trabecular, or solid patterns (a: H+E, ×50; b: H+E, ×200); c: Pheochromocytoma stained with antibodies to chromogranin A (immunoperoxidase, ×200); d: Mitotic rate is 0.5% with Ki-67 (immunoperoxidase, ×200)

2.6 Case 6

A man aged 50 years was diagnosed as having a 9 cm left kidney mass reminiscent of renal cell cancer after a radiologic evaluation. He was referred to the urology department for a radical nephrectomy. The procedure was uneventful and concluded without any operative complication. Pathologic features indicated a pheochromocytoma that was 11 cm × 6.5 cm × 4.5 cm in size. An immunohistologic examination revealed positive chromogranin staining, synaptophysin, and neuron-specific enolase. The patient was discharged five days later, but he was not included in any follow-up program. Five years later, the man was referred to an orthopedic outpatient clinic because of right knee pain. 18F-2-Fluoro-deoxy-D-glucose-positron-emission tomography scans showed an SUVmax of 4.3 for a mass localized at the femur trochanter minor. After local resection of the lesion, a pathologic study revealed a metastatic tumor originating from a pheochromocytoma (see Figure 2).

2.7 Case 7

A woman aged 32 years was admitted with severe headache and a blood pressure of 240/140 mmHg. During a search because of secondary hypertension, an abdominal CT showed a 3 cm enlargement of the left adrenal. Biochemical tests to determine functional hormone secretions were within the normal range. The patient stopped her treatment and went to the surgery department where an adrenal tru-cut biopsy was performed under CT. The biopsy showed that it was pheochromocytoma. A left adrenalectomy was subsequently performed after preparation for PC, and the histologic examination confirmed the diagnosis of pheochromocytoma.

3. DISCUSSION

Since being first described in 1886 by Fränkel, the management and treatment of PC has been a dilemma for physicians.^[9,10] Autopsy studies have shown that a significant proportion of PCs remain undiagnosed during a patient's life. Although 53% of these tumors were reported to go undiagnosed before surgery or autopsy until 1962, after the advent of imaging techniques, this percentage dropped.^[11,12] In addition, masses were more commonly found in women (55.2%) than men (44.8%). In some studies, such differences in sex distribution could be attributed to women having more abdominal imaging and abdominal surgery compared with men. Other studies, however, have reported similar incidences of masses in men and women, based on autopsy findings.^[13,14] In recent years, the misdiagnosis of PC has become uncommon. Misdiagnosis of PC is associated with serious adverse effects, morbidity and mortality. There is also a lack of systemic studies on whether misdiagnosis results in significant morbidities or mortalities caused by unnecessary surgery or lack of preoperative preparation.^[15] Platts et al. published a large study that showed that anesthesia and surgery in the presence of undiagnosed PC was the cause of death in 16 of 62 patients.^[16] In this study, we investigated the misdiagnosis and pitfalls of treatment of PC. Our study showed that the diagnosis of PC is still a challenge, and seven patients were misdiagnosed in our series.

The incidence of PC is less than 0.5% in patients with hypertension; however, it has been demonstrated to account for as much as 4% in patients who present with an adrenal incidentaloma.^[17,18] Conversely, Mannelli *et al.* reported a retrospective ethnic study in Italian patients, of which 11.2% of tumors were incidentally diagnosed, and among these, 62.5% were normotensive.^[19] In our series, hypertension was the presenting symptom in one patient (case 7).

The clinical presentation of PC primarily depends on the type and pattern of catecholamine released from the tumor. PC may present with asymptomatic and unsuspected symptoms;

however, the classic triad of PC presentation is episodic headache, sweating, and palpitation.^[1,9,20] Other symptoms related with PC are breathlessness, anxiety, sense of dread, chest pain, nausea, vomiting, tremors, and paraesthesia.^[21] It should not be forgotten that the subclinical picture does not exclude the potential occurrence of hypertensive crises.^[22,23] In addition to the above-mentioned symptoms and signs, malignant PC may also present with systemic symptoms or clinical manifestations related to metastatic disease, such as pain in bones affected by metastatic spread. Metastases occur most frequently in bones, liver, and lungs.^[10,24] In our series, two patients had a hypertensive crisis during surgery, and others had no symptoms before or after interventions. Additionally, one patient who was not included in any follow-up program presented with left leg pain, which was affected by metastatic PC.

Biochemical tests remain a cornerstone of diagnosis. As a general rule, pheochromocytomas are first established by measurements of free metanephrines (normetanephrine and metanephrine) in plasma and urinary fractionated metanephrines, and are confirmed by specific imaging studies. Urinary measurements of total catecholamines and metanephrines were found to have a sensitivity and specificity of 98% and 98%, respectively. Additionally, measurement of plasma metanephrine levels has a sensitivity of 99% and a specificity of 89%.^[25-27] False positive biochemical test results for PC are common and present particular problems because of the low prevalence of the disease.^[28] For this reason, tests should be repeated to confirm the results.^[15] It should be considered that tricyclic antidepressants, phenoxybenzamine, and panic disorders may result in false positive results.^[1,20]

Metanephrines can be measured using several methods, including high-performance liquid chromatography (HPLC) with electrochemical or mass spectrometric detection and immunoassays, such as radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA).^[29] Although few studies have compared measurement methods, immunoassays significantly underestimate plasma levels of metanephrines compared with HPLC-based methods.^[30] In a study reported by Eisenhofer et al., the amount of catecholamines and metanephrines released are, in general, positively correlated with tumor size.^[31] Conversely, the temporary disappearance of symptoms makes the clinical picture even more misleading because of the extensive internal necrotic and hemorrhagic areas.^[10] The main cause of problems that lead to the misdiagnosis of pheochromocytoma may be silent hormone conditions. However, Lenders *et al.* reported that the combination of different biochemical investigations did not increase diagnostic accuracy.^[21] In our case series, adrenal

biopsy was performed before biochemical investigations in cases 1 and 7. Patients underwent surgery because of the diagnosis of pheochromocytoma after a watchful preoperative preparation for elevated biochemical tests. Adrenalectomy was performed uneventfully after the preoperative preparation for elevated hormone levels in patient 2 who had a hypertensive crisis during a hemorrhoid operation. Patients 4 and 6 underwent surgery in the urology department for renal tumors without any investigation for adrenal diseases. In case 3, the tumor was hormonally silent but underwent surgery because the radiologic images indicated a non-adenoma mass with a high SUV-max level on PET-CT (SUV-max: 7.9). In patient 5, who had a history of breast cancer that was hormonally silent, radiologic images showed a metastatic lesion. Therefore, the patient underwent metastasis surgery.

Imaging tests, such as CT and MRI are useful as the first radiologic approaches after a biochemical diagnosis is confirmed. CT and MRI are sensitive enough to localize most pheochromocytomas larger than 5 mm.^[32] CT and MRI scans have 90%-100% sensitivity and 70%-80% specificity rates.^[10-20] Confirmatory studies that include iodine-123-labeled metaiodobenzylguanidine (¹²³MIBG) or ¹³¹MIBG are recommended because of the limited specificity rates of MRI and CT imaging; however, Adler et al. found that scintigraphic images were not essential if there was no suggestion of familial disease.^[33] ¹²³MIBG is superior to ¹³¹MIBG in terms of physical properties, evaluation of metastasis, quality of images, and sensitivity. ¹²³MIBG scanning and ¹³¹MIBG have specificity of approximately 95%; however, ¹²³MIBG shows a higher sensitivity of 83%-100% compared with ¹³¹MIBG.^[34] Moreover, MIBG has a role in the staging and diagnosis of malignant disease that cannot be detected by CT or MRI.^[35] Guller *et al.* reported that MIBG scan should be performed when a pheochromocytoma is suspected and catecholamine measurements are within normal range.^[36] Another important imaging technique, PET in combination with ¹⁸F-FDG, showed a higher sensitivity of 97%-100%.^[37] Generally, PET scanning is largely reserved for extra-adrenal paragangliomas or particularly large tumors to rule out metastasis.^[29] In our case series, with the exception of case 2, none of the cases were diagnosed with imaging tests. A silent hormone profile and undiagnosed imaging tests were the important causes of pitfalls that led to misdiagnosis of pheochromocytoma.

Every crisis may be the last one for a patient with pheochromocytoma. During the surgical manipulation of PC, massive catecholamine release may occur and result in hypertensive crisis, cardiac arrhythmias, cerebral vascular accident, myocardial infarction or ischemia, pulmonary edema, and multi-organ failure.^[33] An adrenal biopsy is often performed to exclude metastatic disease of the adrenal gland, but the biopsy can be life threatening in the setting of PC. The literature contains numerous case reports from the 1970s to the 1990s of devastating complications related to adrenal biopsy.^[38] The fine-needle aspiration biopsy of a pheochromocytoma may result in hemorrhage, tumor implantation, myocardial infarction, arrhythmia, stroke, hypertensive crisis, and death.^[38,39] Therefore, the possibility of pheochromocytoma should always be ruled out through biochemical tests before a fine-needle aspiration biopsy is undertaken. Given the strong association between imaging features and pheochromocytoma, some experts advocate treatment with an γ - and β -adrenergic blockade and tumor resection in patients with an imaging phenotype of pheochromocytoma, even when the results of biochemical tests for pheochromocytoma are normal.^[39,40]

4. CONCLUSION

Correct diagnosis and management of pheochromocytoma is clinically important because a misdiagnosis leads to high morbidity and mortality secondary to hypertensive crisis. There have been many difficulties in the diagnosis of PC. There is a need for more specific tests for patients who are diagnosed as having PC but whose hormonal investigations are normal. In summary, in this case series we aimed to emphasize the difficulties and faults of diagnosing PC and suggest strategies to prevent repetitions in misdiagnoses.

CONFLICTS OF INTEREST DISCLOSURE

The authors have no potential conflict of interest

Consent

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

ACKNOWLEDGEMENTS

We thank Prof. Servet Karahan for the discussion and suggestions about the diagnosis.

REFERENCES

- [1] Manger WM, Gifford RW Jr. Clinical and experimental pheochromocytoma. Blackwell Science. Cambridge, MA. 1996.
- [2] Whalen RK, Althausen AF, Daniels GH. Extra-adrenal pheochromocytoma. *J Urol.* 1992; 147: 1-10. PMID:1729490
- [3] Lenders JW, Eisenhofer G, Mannelli M, *et al.* Phaeochromocytoma. *Lancet.* 2005; 366: 665-75. [http://dx.doi.org/10.1016/S0140-6736\(05\)67139-5](http://dx.doi.org/10.1016/S0140-6736(05)67139-5)
- [4] Manger WM. Diagnosis and management of pheochromocytoma-recent advances and current concepts. *Kidney International sup.* 2006; 70: 30-5. <http://dx.doi.org/10.1038/sj.ki.5001974>
- [5] Bravo EL, Tagle R. Pheochromocytoma: state of the art and future prospects. *Endocrine Reviews.* 2003; 24: 539-53. PMID:12920154 <http://dx.doi.org/10.1210/er.2002-0013>
- [6] Wooster DL, Mitchell RL. Unsuspected phaeochromocytoma presenting during surgery. *Canadian Anaesthetists Society Journal.* 1981; 28: 471-74. <http://dx.doi.org/10.1007/BF03010359>
- [7] Naderi N, Amin A, Setayesh A, *et al.* Pheochromocytoma-induced reverse takotsuba with rapid recovery of lent ventricular function. *Cardiology Journal.* 2012; 19: 527-31. PMID:23042320 <http://dx.doi.org/10.5603/CJ.2012.0097>
- [8] Doo AR, Son JS, Han YJ, *et al.* Hypertensive crisis caused by electrocauterization of the adrenal gland during hepatectomy. *BMC Surg.* 2015; 15: 11. PMID:25972017 <http://dx.doi.org/10.1186/1471-2482-15-11>
- [9] Mannelli M, Lenders J, Pacak K, *et al.* Subclinical Phaeochromocytoma. *Best Pract Res Clin Endocrinol Metab.* 2012; 26(4): 507-515. PMID:22863392 <http://dx.doi.org/10.1016/j.beem.2011.10.008>
- [10] Pacak K, Linehan WM, Eisenhofer G, *et al.* Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. *Ann Intern Med.* 2001; 134: 315-329. PMID:11182843 <http://dx.doi.org/10.7326/0003-4819-134-4-200102200-00016>
- [11] Krane NK. Clinically unsuspected pheochromocytomas. Experience at Henry Ford Hospital and areview of the literature. *Arch Intern Med.* 1986; 146: 54-57. PMID:3942465 <http://dx.doi.org/10.1001/archinte.1986.00360130064008>
- [12] Sutton M, Sheps SG, Lie JL. Prevalence of clinically unsuspected pheochromocytoma; review of a50-year autopsy series. *Mayo Clin Proc.* 1981; 56: 354-360. PMID:6453259
- [13] Russell RP, Masi AT, Richter ED. Adrenal cortical adenomas and hypertension A clinical pathologic analysis of 690 cases with matched controls and a review of the literature. *Medicine (Baltimore).* 1972; 51: 211-225. <http://dx.doi.org/10.1097/00005792-197205000-00007>
- [14] Grumbach MM, Biller BM, Braunstein GD, *et al.* Management of the clinically inapparent adrenal mass ("incidentaloma"). *Ann Intern Med.* 2003; 138: 424-429. PMID:12614096 <http://dx.doi.org/10.7326/0003-4819-138-5-200303040-00013>
- [15] Yu R, Nissen NN, Chopra P, *et al.* Diagnostic and treatment of pheochromocytoma in an academic hospital from 1997 to 2007. *The American Journal of Medicine.* 2009; 122: 85-95. PMID:19114176 <http://dx.doi.org/10.1016/j.amjmed.2008.08.021>
- [16] Platts JK, Drew PJ, Harvey JN. Death from phaeochromocytoma: lessons from a post-mortem survey. *JR Coll Physicians Lond.* 1995; 29(4): 299-306. PMID:7473324
- [17] 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. <http://dx.doi.org/10.1097/00005792-199101000-00004>
- [18] Mantero F, Terzolo M, Arnaldi G, *et al.* A survey on adrenal incidentalomain Italy. Study Group on Adrenal Tumors of the Italian Society of Endocrinology. *J Clin Endocrinol Metab.* 2000; 85: 637-644. PMID:10690869
- [19] Mannelli M, Ianni L, Cilotti A, *et al.* Pheochromocytoma in Italy: a multicentric retrospective study. *Eur J Endocrinol.* 1999; 141: 619-624. PMID:10601965 <http://dx.doi.org/10.1530/eje.0.1410619>
- [20] Manger WM. The vagaries of pheochromocytomas. *Am J Hypertens.* 2005; 18: 1266-1270. PMID:16202846 <http://dx.doi.org/10.1016/j.amjhyper.2005.06.026>
- [21] Lenders JW, Pacak K, Walther MM, *et al.* Biochemical diagnosis of pheochromocytoma: which test is best? *JAMA.* 2002; 287: 1427-34. PMID:11903030 <http://dx.doi.org/10.1001/jama.287.11.1427>
- [22] Song G, Bonnie NJ, Benjamin MY, *et al.* Risk of catecholamine crisis in patients undergoingresection of unsuspected pheochromocytoma. *Int Braz J Urol.* 2011; 37: 35-41. PMID:21385478 <http://dx.doi.org/10.1590/S1677-55382011000100005>
- [23] Shen SJ, Cheng HM, Chiu AW, *et al.* Perioperative hypertensive crisis in clinically silent pheochromocytomas: report of four cases. *Chang Gung Med J.* 2005; 28: 44-50. PMID:15804148
- [24] Parenti G, Zampetti B, Rapizzi E, *et al.* Updated and New Perspectives on Diagnosis, Prognosis, and Therapy of Malignant Pheochromocytoma/Paraganglioma. *Journal of Oncology.* 2012; 2012: 872713. PMID:22851969 <http://dx.doi.org/10.1155/2012/872713>
- [25] Zelinka T, Widimsky J, Weissnerova J. Diminished circadian blood pressurerhythm in patients with asymptomatic normotensive pheochromocytoma. *Physiol Res.* 2001; 50: 631-34. PMID:11829326
- [26] Sawka AM, Jaeschke R, Singh RJ, *et al.* A comparison of biochemical tests for pheochromocytoma: Measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. *J Clin Endocrinol Metab.* 2003; 88: 553-58. PMID:12574179 <http://dx.doi.org/10.1210/jc.2002-021251>
- [27] Symthe GA, Edwards G, Graham P, *et al.* Biochemical diagnosis of pheochromocytoma by simultaneous measurement of urinary excretion of epinephrine and norepinephrine. *Clin Chem.* 1992; 38: 486-92.
- [28] Harding JL, Yeh M, Bruce R, *et al.* Potential pitfalls in the diagnosis of phaeochromocytoma. *Med J of Australia.* 2005; 182(12): 637-639. PMID:15963022
- [29] Singer J, Koch C, Kassahun W. A patient with a large recurrent pheochromocytoma demonstrating the pitfalls of diagnosis. *Nat Rev Endocrinol.* 2011; 7: 749-55. PMID:21894215 <http://dx.doi.org/10.1038/nrendo.2011.132>
- [30] Pillai D, Callen S. Pilot quality assurance programme for plasma metanephrines. *Ann Clin Biochem.* 2010; 47: 137-42. <http://dx.doi.org/10.1258/acb.2009.009153>
- [31] Eisenhofer G, Lenders JWM, Goldstein DS, *et al.* Pheochromocytoma catecholamine phenotypes and prediction of tumor size and location by use of plasma free metanephrines. *Clin Chem.* 2005; 51: 735-44. PMID:15718487 <http://dx.doi.org/10.1373/clinchem.2004.045484>
- [32] Pacak K, Goldstein DS, Doppman JL, *et al.* A "pheo" lurks: novel approaches for locating occult pheochromocytoma. *J ClinEndocrinol-Metab.* 2001; 86: 3641-6.
- [33] Adler JT, Meyer-Rochow G, Chen H, *et al.* Pheochromocytoma: current approaches and future directions. *The Oncologist.* 2008; 13: 779-93. PMID:18617683 <http://dx.doi.org/10.1634/theoncologist.2008-0043>
- [34] Ilias I, Pacak K. Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. *J Clin Endocrinol*

- Metab. 2004; 8: 479-91. PMID:14764749 <http://dx.doi.org/10.1210/jc.2003-031091>
- [35] Shapiro B. Ten years of experience with MIBG applications and the potential of new radiolabeled peptides: A personal overview and concluding remarks. Q J Nucl Med. 1995; 39: 150-55. PMID:9002776
- [36] Guller U, Turek J, Eubanks S, *et al.* Detecting pheochromocytoma: defining the most sensitive test. Annals of Surgery. 2006; 243: 102-7. PMID:16371743 <http://dx.doi.org/10.1097/01.sla.0000193833.51108.24>
- [37] Shulkin BL, Thompson NW, Shapiro B, *et al.* Pheochromocytomas: Imaging with 2-fluorine-18fluoro-2-deoxy-D-glucose PET. Radiology. 1999; 212: 35-41. PMID:10405717 <http://dx.doi.org/10.1148/radiology.212.1.r99j13035>
- [38] Vanderveen KA, Thompson MS, Callstrom RM, *et al.* Biopsy of pheochromocytomas and paragangliomas: potential for disaster. Surgery. 2009; 146: 1158-1166. PMID:19958944 <http://dx.doi.org/10.1016/j.surg.2009.09.013>
- [39] Assalia A, Gagner M. Laparoscopic adrenalectomy. Br J Surg. 2004; 91: 1259-74. PMID:15376201 <http://dx.doi.org/10.1002/bjs.4738>
- [40] Young FW. The incidentally discovered adrenal mass. New Engl J Med. 2007; 356: 601-610. PMID:17287480 <http://dx.doi.org/10.1056/NEJMcp065470>