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CASE

Epinephrine-Secreting Cystic Pheochromocytoma Presenting with an Incidental Adrenal Mass

A Case Report and a Review of the Literature

Cihangir Erem,[1] Mustafa Kocak,[1] Halil Önder Ersoz,[1] Safak Ersoz,[2] and Yusuf Yucel[3]

[1]Department of Internal Medicine, Division of Endocrinology and Metabolism, [2]Department of Pathology, and [3]Department of General Surgery, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey

Cystic adrenal masses are a relatively rare condition, and are usually nonfunctioning and asymptomatic. Differential diagnosis includes pheochromocytoma (PHEO) and adrenal carcinoma; 8–10% of patients with PHEO may be completely asymptomatic. Moreover, fewer than 10% of PHEOs secrete pure epinephrine. We report a case of a E-secreting pure cystic PHEO presenting with an incidental adrenal mass. A 49-year-old Turkish woman was hospitalized at Farabi Hospital for further examinations of a right adrenal cystic mass with a thick wall that was incidentally discovered by abdominal ultrasonography during examination for nausea, vomiting, headache, and angina-like chest pain in another hospital. On admission, her blood pressure was 100/60 mmHg. Tension Holter monitoring revealed paroximal hypertension (178/136 mmHg) and hypotension (78/54 mmHg) attacks. Of urinary catecholamines and its metabolites, only urine metanephrine was markedly increased, despite a urine epinephrine level near the upper limit of normal ranges. Abdominal computed tomography and magnetic resonance imaging studies revealed a cystic round tumor approx 5 cm in diameter, located in the right adrenal gland. Right adrenalectomy was performed; the surgical specimen revealed pure cystic PHEO. Postoperatively, the urine metanephrine level returned to normal range and urine epineprine level was decreased approx 60%. In conclusion, a diagnosis of E-secreting PHEO should be considered in patients with nonspecific symptoms, presenting with an incidental cystic adrenal mass, even in the absence of hypertension.

Key Words: Cystic pheochromocytoma; epinephrine; incidental adrenal mass.

Introduction

Pheochromocytoma (PHEO), a catecholamine-producing tumor arising in the adrenal medulla or sympathetic ganglia, has an estimated incidence of two to eight cases per million persons annually *(1,2)*. It can present clinically as hypertension, spells (of hypertension, palpitation, headache, or other symptoms), or as an incidentally discovered adrenal mass seen on imaging studies *(2,3)*; 8–10% of patients with PHEOS are asymptomatic *(4)*. Prompt diagnosis is important because resection of the tumor dramatically reverses the clinical symptoms and may cure the hypertension *(5)*. A missed or delayed diagnosis may cause considerable morbidity and mortality *(5)*.

PHEOs secrete a variety of catecholamines, of which norepinephrine (NE) is usually predominant. Pure epinephrine (E)-secreting tumors are rare *(6)*. Fewer than 10% of PHEOs secrete E, which is 10 times more metabolically active than NE *(7)*.

Cystic adrenal masses are relatively rare lesions and most of them are nonfunctioning and asymptomatic *(6)*. Differential diagnosis includes adrenal cyst, pseudocyst, adrenal carcinoma, and PHEO *(4,8,9)*. PHEOs and adrenal carcinomas often have a functional component, and clinical symptoms and biochemical assays should help guide the diagnosis of these lesions *(10)*.

We describe a case of a E-secreting pure cystic PHEO presenting with an incidental adrenal mass.

Case Report

A 49-yr-old Turkish woman was hospitalized at Farabi Hospital for further examination of a right adrenal cystic mass with a thick wall that was incidentally discovered by abdominal ultrasonography (Fig. 1) during examination for nausea, vomiting, headache, and angina-like chest pain in another hospital. Her medical history and review of systems were otherwise unremarkable. On admission, her blood pressure was 100/60 mmHg. Electrocardiogram was normal. Tension Holter monitoring revealed paroximal hypertension (178/136 mmHg) and hypotension (78/54 mmHg)

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Author to whom all correspondence and reprint requests should be addressed: Prof. Dr. Cihangir Erem, K.T.Ü. Tip Fakültesi, Iç Hastaliklari Anabilim Dali, 61080, Trabzon/Turkey. E-mail: cihangirerem@hotmail.com; cihangirerem@netscape.net

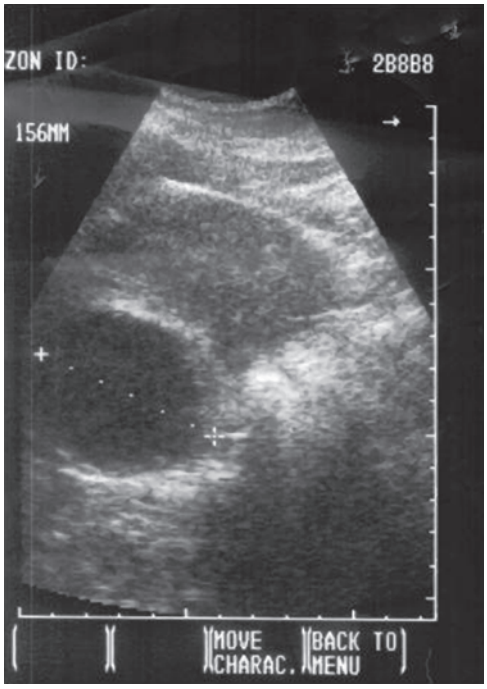

Fig. 1. Abdominal ultrasonography obtained at the level of the right adrenal fossa shows a thick-walled (8 mm), well-defined anechoic cystic mass, 57 mm in diameter.

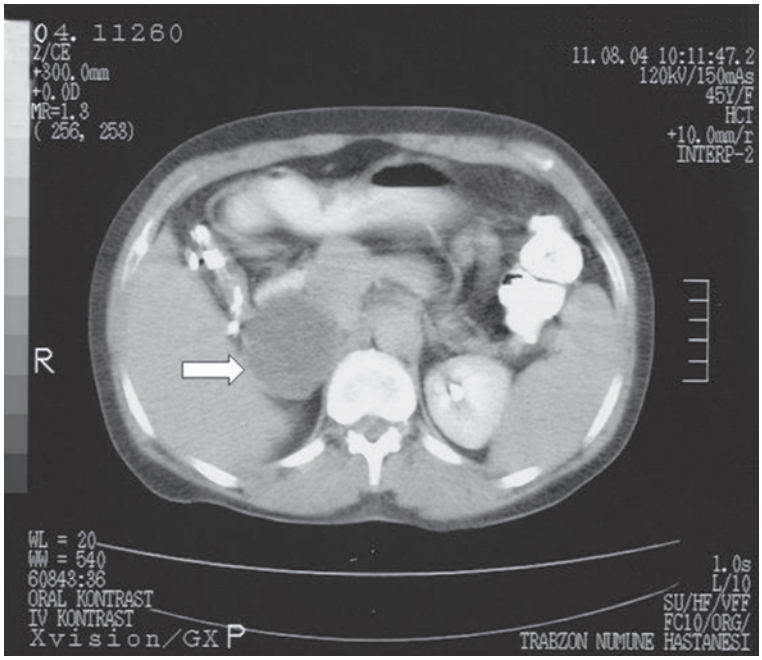

Fig. 2. Contrast-enhanced axial CT scan shows a well-defined hypodense cystic mass at the right adrenal gland (arrow).

attacks. Laboratory values were as follows: urine norepinephrine 26 μg/24 h (normal: 15–80), urine epinephrine 18.5 μg/24 h (normal: 0.5–20), urine normetanephrine 412 μg/24 h (normal: 88–444), urine metanephrine 1373 and 1990 μg/24 h, repeated twice (normal: 52–341), urine vanillylmandelic acid 4.3 mg/24 h (normal: 3–9), urine dopamine 295 μg/24 h (65–400), homovanillic acid 8.1 mg/24 h (normal: 1.4–8.8). Serum cortisol and urinary free cortisol levels were normal (10.6 μg/dL and 15.5 μg/d, respectively). The levels of serum calcitonin, intact parathyroid hormone (iPTH), carcinoembryonic antigen, alpha-fetoprotein, serum aldosterone concentrations, plasma DHEA-S, and plasma renin activity were within normal ranges. Abdominal computed tomography showed a well-demarcated cystic mass (50 × 50 mm) with a thick wall in the region of the right adrenal gland (Fig. 2). Abdominal magnetic resonance imaging (MRI) revealed a well-demarcated hyperintense mass measuring 50 × 50 mm, located in right adrenal gland, on T_1 and T_2-

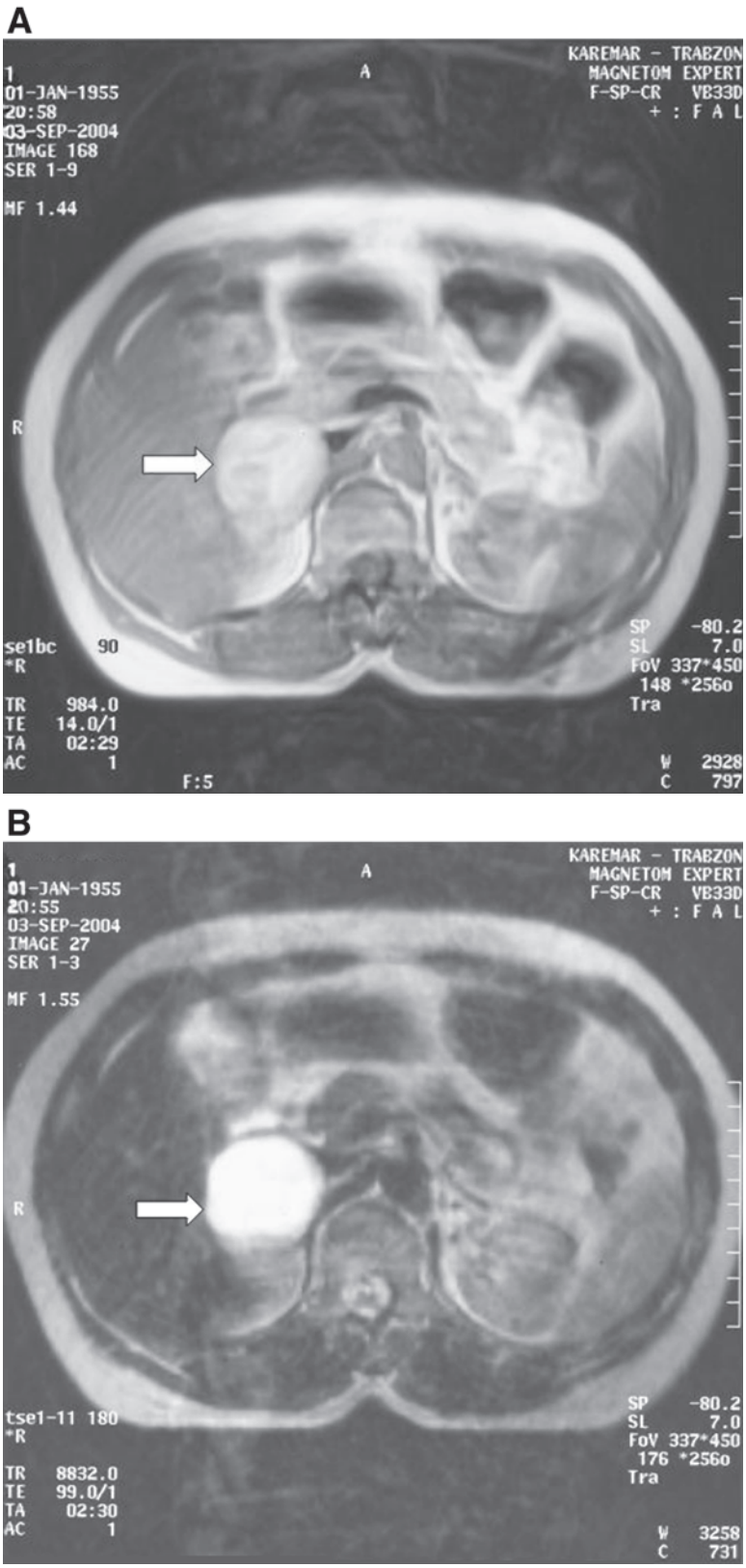

Fig. 3. (**A**) T_1-weighted and (**B**) T_2-weighted magnetic resonance images reveal high signal intensity of the cystic PHEO at the right adrenal gland (arrows). Hyperintensity in tumor is more prominent at T_2-weighted MR image.

weighted sequences (Fig. 3). Out-of-phase MR image did not show significant signal loss in the lesion when compared with in-phase MR image. A ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) scan revealed uptake within tumor in the right adrenal gland. A diagnosis of E-secreting pure cystic right adrenal PHEO was made. After adequate α-receptor block-

Fig. 4. Gross pathologic appearance of postoperative right cystic adrenal PHEO. It is encapsulated, 50 × 50 mm in diameter, and weighs 50 g (**A**), and on section, reddish brown mass with evidence of hemorrhage (**B**).

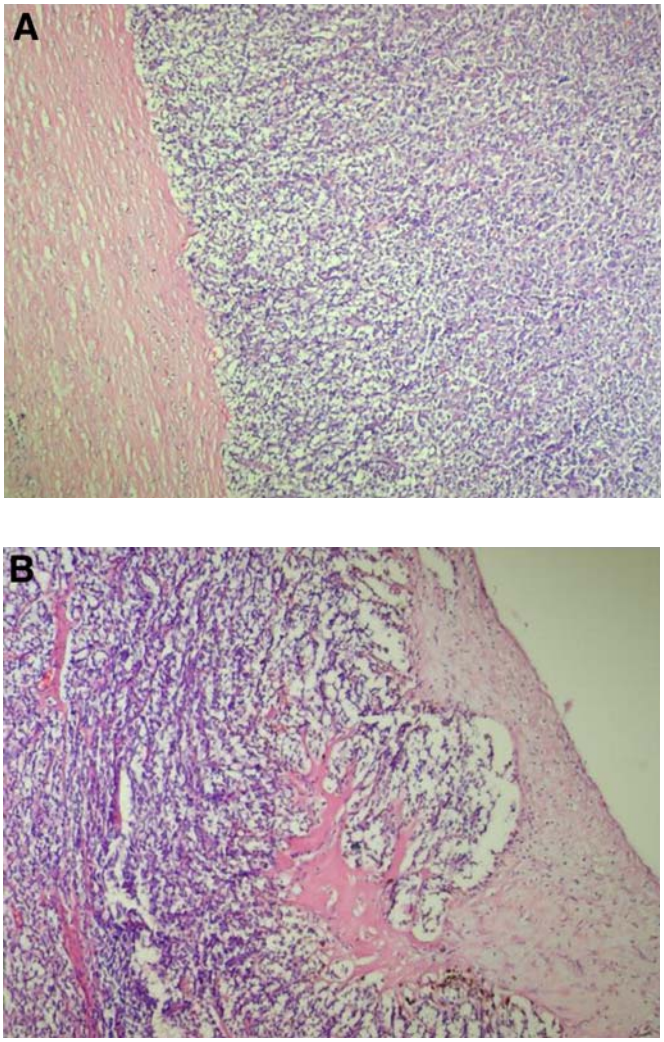

Fig. 5. Microscopic appearance of postoperative right adrenal tumor. (**A**) The tumor was surrounded by a thick fibrous capsule. There was no evidence of vascular invasion and infiltration of the capsule by the tumor. (Hematoxylin and eosin staining, original magnification ×100.) (**B**) The tumor cells are characteristically arranged in well-defined nests ("Zellballen") bound by a delicate fibrovascular stroma. The cells have a finely granular cytoplasm. The nuclei are usually round or oval with prominent nucleoli. Hemosiderin pigment, including hemorrhage and fibrosis was abundant. (Hematoxylin and eosin staining, original magnification × 100.)

ade with phenoxybenzamine, a β-adrenoceptor blocker (propranolol) was added to the therapy. Normotension was reached on tension Holter monitoring. Right adrenalectomy was performed by the transabdominal route. Once completely excised, gross clinical examination of the mass revealed a 5.5 cm spherical, fluctuant cystic mass (Fig. 4). Gross histopatological evaluation revealed a 50 g, unilocular, smooth-walled cyst filled with hemorrhagic fluid, containing a reddish brown fluid. Microscopic examination of the mass demonstrated fibrinous material and hemosiderin pigment within the cystic cavity. There was no evidence of vascular invasion or infiltration of the capsule by the tumor (Fig. 5A). Pathological examination of the cyst wall revealed PHEO (Fig. 5B). The tumor cells had abundant cytoplasm and central nuclei separated with highly vascularized thick fibrous septa. Cortical atrophy adjacent to the tumor was observed. The chief cells were strongly positive for chromogranin A and synaptophysin on immunohistochemical study. The final histopatological diagnosis was cystic PHEO with hemorrhagic necrosis. Urine metanephrine level returned to normal range (161 μg/24 h) on postoperative d 7. Urinary E level decreased from preoperative 18.5 μg/24 h to postoperative 7.2 μg/24h The patient's postoperative course was uncomplicated, and she was discharged home on postoperative d 12.

Discussion

PHEO is a rare tumor of chromaffin cells in the adrenal medulla or sympathetic ganglia. Its clinical hallmark is sustained or intermittent hypertension often associated with par-

oximal symptoms *(1)*. PHEOs are highly vascular tumors, and most are unilateral and solitary. A "Rule of 10s" has been attributed to cystic PHEOs, with an approximate 10% incidence of familial occurrence, malignant phenotype, extraadrenal location, bilateral or multiple tumor formation, without blood pressure elevation, childhood onset, and recurrence after resection *(10,11)*. More recently, it was noted that PHEO is connected with germ-line mutation, especially with nonsyndromic PHEO *(12)*. Close to 90% of PHEOs originate in the medulla of the adrenal glands. The remaining 10% of PHEOs are extraadrenal, or more commonly known as *catecholamine-secreting paragangliomas*.

Patients with PHEO have a variety of symptoms attributable to periodic increases in the secretion of catecholamines. In a patient with hypertension, the usual triad of headaches, palpitations, and sweating strongly suggests the presence of PHEO. Less frequent symptoms are pallor, nausea, abdominal and chest pain, fatigue, flushing, and tremor *(13)*. In one study *(14)*, the symptomatic triad of headache, sweating attacks, and tachycardia in a hypertensive patients was found to have a sensitive of 90.9% and specifity of 93.8%. However, about 8% of patients may be completely asymptomatic; such patients are usually those with familial forms of the disease *(15)*.

The catecholamines secreted by these tumors (primarily NE and E) are responsible for the clinical manifestations of PHEOs. Hypertension is often resistant to standard medical therapy. There is no correlation between circulating levels of the catecholamines or even existence of hypertension in these patients. In general, the hypertension is paroximal in 48% of patients, persistent in 29%, and 13% have normal blood pressure. NE-secreting tumors are usually associated with sustained hypertension. Tumors that secrete relatively large amounts of E together with NE are associated with episodic hypertension. Pure E-producing tumors can produce hypotension rather than hypertension *(16)*. Large (>50 g) cystic PHEOs are often asymptomatic because the secreted catecholamines are metabolized within the tumor and, therefore, only a small amount, if any, of free catecholamines is released into the circulation *(15)*. In the present case, normal urinary E level may be due to this mechanism.

When a catecholamine-producing tumor such as a PHEO or paraganglioma is clinically suspected, the appropriate initial screening study is a 24-h urine collection to evaluate for levels and its metabolites, such as metanephrine and vanillylmandelic acid. In addition to urinary levels, sometimes, serum catecholamine levels may also be used. After confirmation of elevated levels of catecholamine or its metabolites, diagnostic imaging, using CT and MRI, is indicated for tumor localization *(10,11,13)*. Because most PHEOs involve the adrenal gland, the abdomen should be the first area evaluated by imaging, but only after a biochemical diagnosis has been made. In up to 5% of abdominal imaging studies, an adrenal mass is found, but in most cases it is an incidental adenoma unrelated to the patient's symptoms *(13)*. Either CT or MRI scanning can detect tumors as small as 0.5 cm in diameter. An advantage of MRI is that the PHEO appears as a bright (hyperintense) mass on a T_2-weighted image *(1,13)*. Moreover, the imaging phenotype consistent with PHEO includes enhancement with iv contrast medium on CT, cystic and hemorrhagic changes, variable sizes, and the possibility of bilateral tumors *(17)*. Occasionally, despite a biochemical diagnosis, imaging techniques do not reveal a PHEO. In such cases, scanning with ^{131}I-metaiodobenzylguanidine may be useful *(18)*, because it is concentrated in PHEOs.

Cystic PHEOs are extremely rare lesions, and they are often not accurately diagnosed before attempts at surgical resection. In contrast to patients with solid PHEOs, patients with cystic PHEOs may not show typical clinical manifestations or have elevated urine levels of catecholamine metabolites *(19)*. There are 17 case reports of pure cystic PHEOs reported in the world literature *(10,11,19–31)*. The reported cases are evenly distributed between men and women, with the mean age at diagnosis being 49 yr (range, 14–69 yr). In the six patients who were symptomatic on presentation, symptoms and signs included the classic triad of hypertension, sweating, and headache, as well as vague complaints of nausea, abdominal pain, or anxiety *(10,20,21,24,29,31)*. In one case, the patient presented with flank pain and hematuria *(24)*, and another presented with urinary frequency *(29)*. In seven cases, the patients were normotensive, preoperatively *(4,11,19,20,26,27,31)*. Urinary catecholamines were elevated in 8 of the 17 cases *(4,10,20–22,27,30,31)*. In seven of the cases, the diagnosis of PHEO was not suspected until the time of resection, when hemodynamic instability occurred *(20,22–24,26,28)*. There were 10 cases where the diagnosis of cystic PHEO was suspected preoperatively *(4, 10,21,22,25,27,29–31)*. To our knowledge, the present case is a first report of pure E-secreting pure cystic PHEO in the English literature. In our case, urinary E level was near the upper limit of normal ranges, despite its urine metabolite, metanephrine, levels were prominently increased. But, postoperatively urinary E levels were decreased.

The definitive treatment of PHEO is surgical excision. For most intraadrenal PHEOs, an adrenalectomy is performed. Preoperatively, these patients undergo adrenergic blockade to avoid any complications from release of catecholamines from the PHEO during surgery. The most widely used agent is phenoxybenzamine, a nonspecific alpha-adrenergic-receptor antagonist. It directly inhibits the synthesis of catecholamines. A beta-adrenoceptor blocker is added to oppose the reflex tachycardia often associated with alpha blockade. Propranolol, 10–40 mg orally four times daily, is effective. After adequate medical blockade and hydration, surgical excision of the PHEO has been performed through a transabdominal incision. Patient survival rates of 97.7–100% are usual after such procedures *(32)*. Residual nonparoxysmal hypertension is found in 27–38% of patients after tumor removal *(33)*.

In conclusion, a diagnosis of E-secreting PHEO should be considered in patients with nonspecific symptoms, and presenting with a incidental cystic adrenal mass, even in the absence of hypertension.

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