Case Report
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COMPOSITE ADRENAL PHEOCHROMOCYTOMA-GANGLIONEUROMA IN AN ADULT PATIENT

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Abstract

Background. Composite adrenal pheochromocytoma-ganglioneuromas (PHEO-GNs) are well-defined neoplasms of the adrenal medulla, consisting of both endocrine and neural components. They are extremely rare. To date, only 46 cases have been reported in the English literature.

Case report. We describe an adult case of endocrinologically active adrenal composite PHEO-GN diagnosed in a 62-year-old male patient with history of dizziness, headache, nausea, vomiting, and uncontrolled hypertension including intermittant hypertension attacks. On physical examination, he had a blood pressure (BP) of 170/110 mmHg. 18-fluorodeoxyglucose positron emission tomography-computed tomography showed a right adrenal tumor with increased metabolic activity. Urinary levels of catecholamines and their metabolites were prominently elevated. Right adrenalectomy was performed for treatment purposes. The histological diagnosis of the resected tumor was composite adrenal PHEO-GN.

Conclusions. Composite adrenal PHEO-GN is a rare entity and preoperative diagnosis is difficult. Its hormonal activity and imaging characteristics are frequently very similar to those of other adrenal tumors, especially pure PHEO and adrenal carcinoma. Therefore, careful evaluation by endocrine tests and multiple imaging procedures are needed for providing a differential diagnosis. However, definitive diagnosis composite adrenal PHEO-GN is established by histological and immunochemical studies. To our knowledge, the present case is the first report that describes composite adrenal PHEO-GN in a patient from Turkey. We discuss this case and review the literature on this unusual entity.

Key words: Composite adrenal medullar tumor, pheochromocytoma, ganglioneuroma, hypertension.

INTRODUCTION

Pheochromocytomas (PHEOs) are rare catecholamine-secreting tumors that arise from chromaffin tissue within the adrenal medulla and extra-adrenal sites (1-4). Because of excess secretion of the hormones: epinephrine (E), norepinephrine (NE), dopamine, and others, patients with PHEO often

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experience symptomatic attacks characterised by severe hypertension, profuse sweating, palpitations, and headaches (2, 3, 5).

Ganglioneuromas (GNs) are rare benign, well-differentiated and slow-growing neoplasms arising from neural crest tissue and are composed of mature ganglion cells and Schwann's cells in a fibrous stroma (6, 7). Characteristically, GNs do not secrete excess catecholamines or steroid hormones. They are generally considered to be nonsecretory (hormonally silent or inactive), and can therefore be asymptomatic even when the size of tumor is large (8, 9). However, some GNs are endocrinologically active, and secrete catecholamines and their metabolites. (7, 10). Although both of the two types of tumor (PHEO and GN) are relatively uncommon, proper diagnosis and treatment are currently available (3, 6, 11).

Composite adrenal PHEO-GN is a well-defined neoplasm of the adrenal medulla and the tumor consists of both endocrine and neural components (12). Histopathologically, the endocrine portion is that of a PHEO, whereas the neural portion has been reported as GN. Composite adrenal PHEO-GN is extremely rare. To date, only 46 cases have been reported in the English literature (4, 12-25). It is difficult to diagnose these tumors precisely as composite adrenal PHEO-GN before surgery. Definitive diagnosis is made by histological examination. Assessment and management of the composite adrenal PHEO-GNs are similar to those of other adrenal tumors. In this report, we present an adult case of composite adrenal PHEO-GN diagnosed in a 62-year-old male patient. Histopathological examination of the adrenal mass confirmed the diagnosis.

CASE REPORT

A 62-year-old Turkish man was hospitalized at our hospital for further examinations of a right adrenal solid mass, measuring 5.5 cm in diameter, that was discovered by abdominal magnetic resonance imaging (MRI) performed elsewhere for a 1-month history of dizziness, headache, nausea, vomiting, and uncontrolled hypertension including intermittent hypertension attacks (200/100 mmHg). Medical history included hypertension and diabetes mellitus for 3 years managed with ramipril (5 mg/d), metoprolol (50 mg/d) and gliclazide modified release (90 mg/d). Hypertension could not be controlled with a combination of above antihypertensive drugs. On physical examination (PE), he had a blood pressure (BP) of 170/110 mmHg, a regular pulse of 72 beats/min, and a weight of 82 kg at a height of 170 cm. He had no features of Cushing's syndrome or virilization. Grade 1 hypertensive retinopathy was found on examination of fundus. The remainder of PE was within normal. Tension Holter monitoring revealed intermittent paroxysmal hypertension attacks (220/110 mmHg). Echocardiography showed left ventricle hypertrophy. Routine laboratory tests were normal. Laboratory values were as follows: urine norepinephrine (NE): 904 μg/24 h (normal: 20-81), urine

epinephrine (E): 201 μg/24 h (normal: 2.0–22), urine normetanephrine: 3300 μg/24 h (normal: 88–444), urine metanephrine: 2880 μg/24h (normal: 52–341), urine vanillylmandelic acid (VMA): 25.7 mg/24 h (normal: 1.8–6.7), urine dopamine: 353 μg/24 h (normal: 40–400) and homovanillic acid (HVA): 9.02 mg/24 h (normal:0.5–6.2). The results of other endocrine tests, including the plasma aldosterone concentration (PAC), plasma renin activity (PRA), PAC/PRA ratio, intact parathyroid hormone (iPTH), serum calcitonin, cortisol and ACTH levels, diurnal cortisol rhythms, 24-hour urinary free cortisol and androgenes, were within normal ranges.

Abdominal computed tomography (CT) showed a well-demarcated, homogeneous, hypodense right adrenal solid mass (4.9×4.5×4.9 cm). In unenhanced CT scan, density of mass was 40 Hounsfield unit (HU), consistent with a nonadenomatous mass. There were no features suggesting the invasion of surrounding structures, or enlarged lymph nodes.

Fluorine 18-fluorodeoxyglucose positron emission tomography-CT (^{18}F-FDG-PET-CT) showed a right adrenal tumor with increased metabolic activity (SUVmax= 5.96) (Fig. 1). A ^{131}Iodine-metaiodobenzylguanidine (^{131}I-MIBG) scan could not be performed.

From these findings, we suspected the tumor to be a PHEO as a higher probability or adrenal carcinoma as a lower probability arising from the right adrenal gland. Following the administration of adequate α-receptor blocking agents with phenoxybenzamine 80 mg/d, a β-adrenoceptor blocker (propranolol, 80 mg/d) was added to the therapy. Normotension was reached on tension Holter monitoring. Right adrenalectomy was performed by the transabdominal route under general anesthesia. Findings on surgical pathology examination were consistent with composite adrenal PHEO-GN. The weight of the resected right adrenal

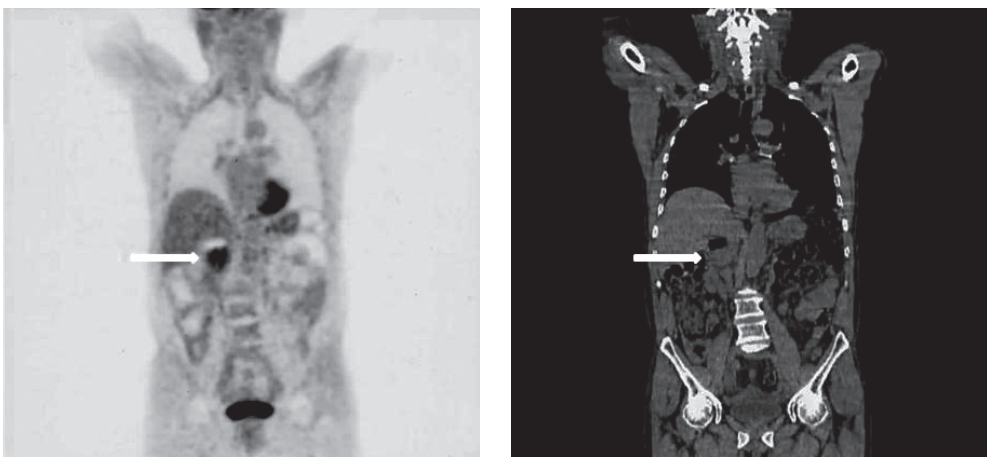

Figure 1. ^{18}F-FDG-PET-CT shows increased tracer uptake of right adrenal lesion, measuring 4.5× 4.5×4.2 cm, with a standardized uptake value (SUVmax) of 5.96, suggestive of nonadenomatosis adrenal tumor (arrows).

gland was 69 g and contained a tumor measuring 6×5×4 cm in dimension. It was encapsulated. The tumor was well-circumscribed with a thin rim of adrenal cortical tissue present at the periphery. The cut surface was brown-gray color with patchy, reddish focal hemorrhage areas (Fig. 2A). Histologically, the tumor consisted of two irregularly distributed distinct patterns (Fig. 2B).

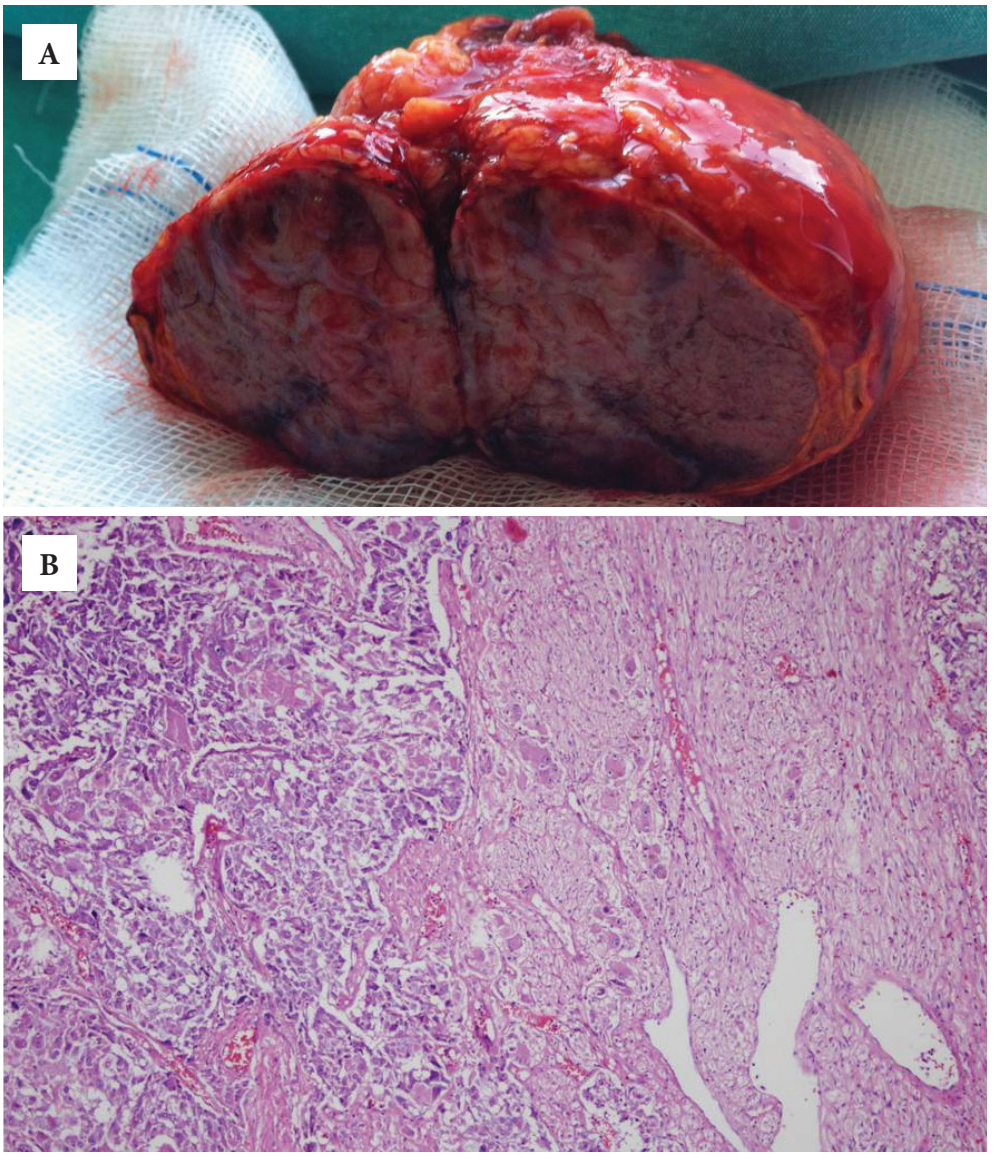

Figure 2. A. Gross pathological appearance of postoperative right adrenal tumor. It is encapsulated, 6×5×4 cm in dimention. The cut surface of the tumor was brown-gray color with patchy, reddish focal hemorrhage areas. **B.** Pheochromocytoma (left) and ganglioneuroma (right) components of adrenal medullar tumor are seen (hematoxylin and eosin staining, original magnification × 100).

The pheochromocytoma component of the tumor contained nests of large, polygonal, and pleomorphic chief cells with granular basophilic cytoplasm and round to oval nuclei (Zellballen pattern) with atrophic adrenal cortical tissue was present at the periphery of the neoplasm (Fig. 2C). The GN component of the tumor contained proliferation of spindled Schwanian cells with the presence of large ganglion cells with eccentrically located nuclei with prominent nucleoli (Fig. 2D). Immunohistochemical studies were performed. The cells of PHEO exhibited focal positive immunoreactivity for synaptophysin and chromogranin A. The spindled Schwann cell component (GN) showed diffuse expression of S-100 protein and neurofilament (Fig. 2E). The specimen did not show any evidence of malignant degeneration histologically. The tumor was diagnosed as a composite adrenal PHEO-GN. Postoperative course was uneventful, and no recurrence was detected at the 6 months follow-up visit. His blood pressure was normal with ramipril (5 mg/d) and metoprolol (50 mg/d). Also, urinary catecholamines and their metabolites were normal.

DISCUSSION

In this report, we presented a case of composite adrenal PHEO-GN

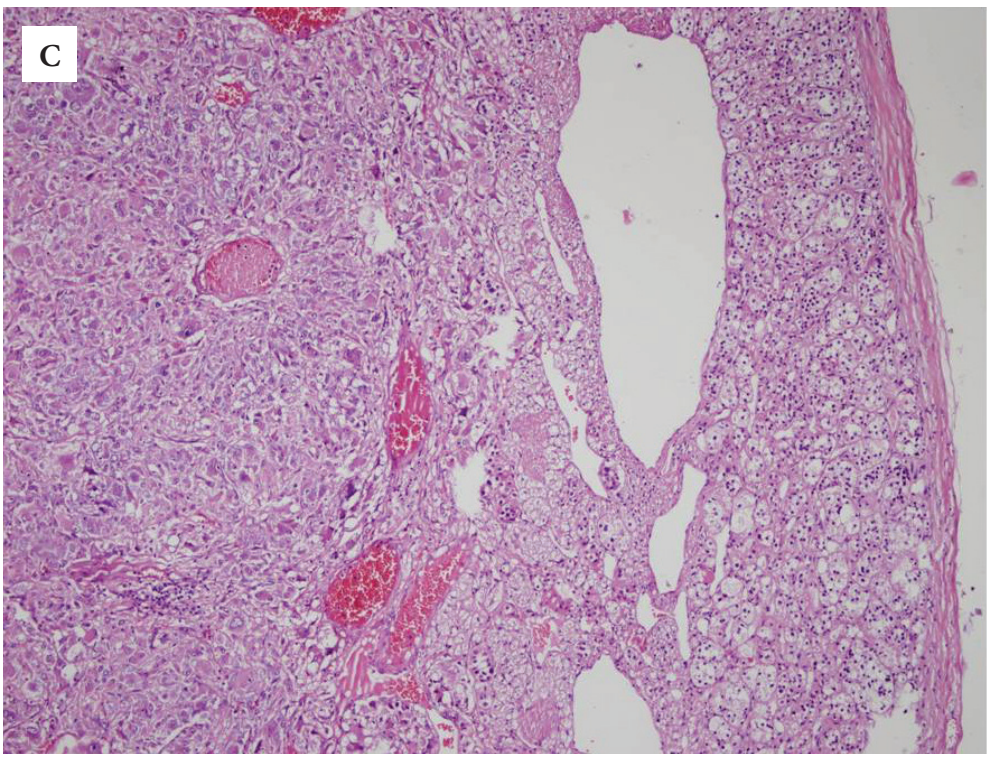

Figure 2. C. The tumor cells in pheochromocytoma consisted of abundant cytoplasm and central nuclei within the highly vascularized fibrous septa (Zellballen pattern) with atrophic adrenal cortical tissue adjacent to neoplasm (hematoxylin and eosin staining, original magnification × 100).

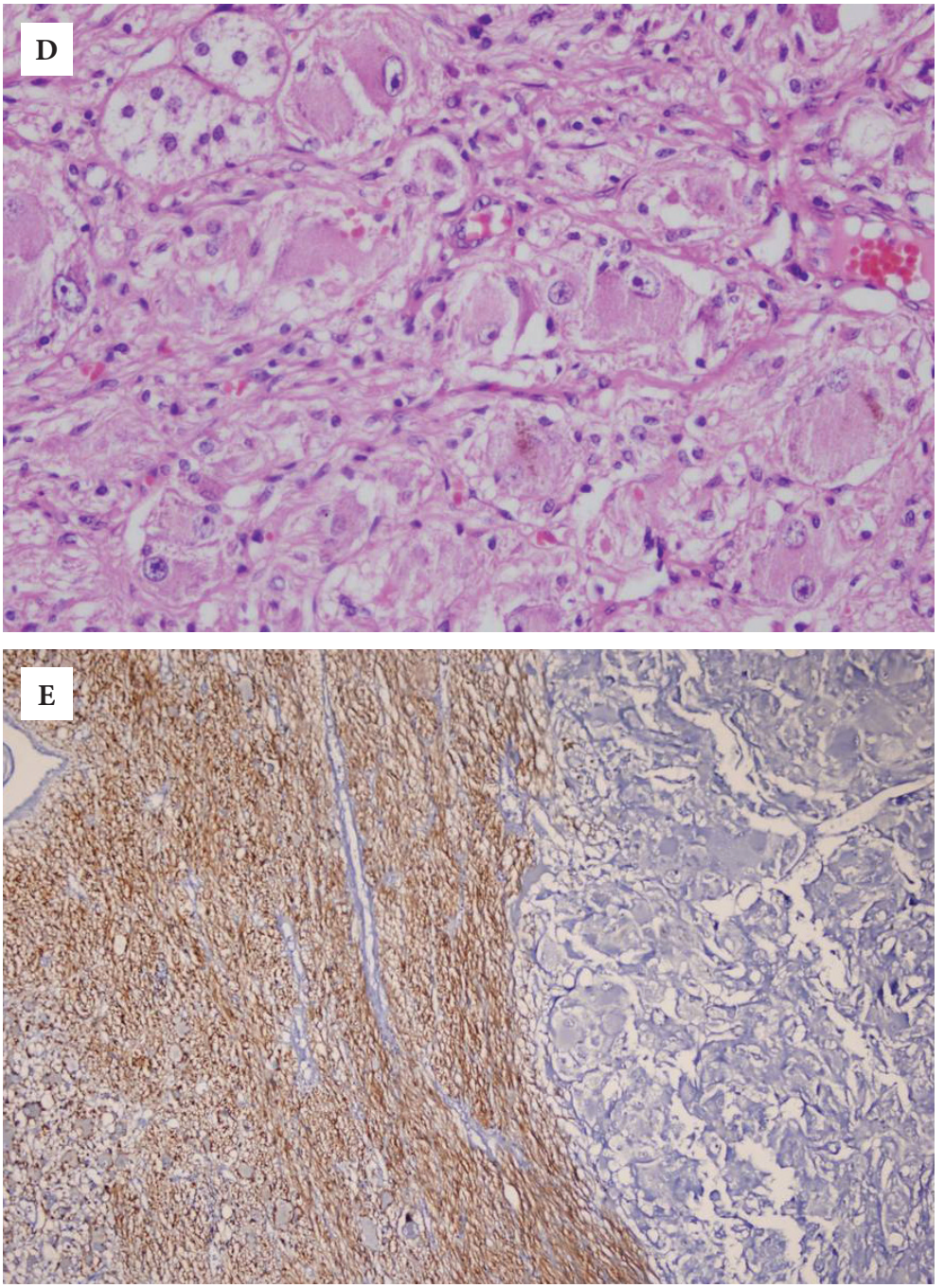

Figure 2. D. Histologic appearance of GN component of the tumor, showing proliferation of spindled Schwanian cells with the presence of large ganglion cells with eccentrically located nuclei with prominent nucleoli (hematoxylin and eosin staining, original magnification × 200). **E.** Spindle-shaped Schwannian cells-rich stroma stained positive for S-100 protein (immunoperoxidase staining, ×100).

in a 62-year old male patient. To our knowledge, our case is the first report that describes composite adrenal PHEO-GN from Turkey.

The adrenal masses may be adrenocortical adenomas and carcinomas, cysts, myelolipomas, pheochromocytomas, ganglioneuromas and adrenal metastases from other malignant tumors (3). Composite adrenal PHEO-GNs are extremely rare; fewer than 50 cases have been reported in the English medical literature (4, 12-26). As reported by Khan and colleagues, they have a variable size (1.0-15 cm, with the average being 4 to 6 cm) at presentation (18). The patients ranged from 32 to 82-years-old, with the majority in the age range of 40 to 60 years, and these tumors occurred with approximately equal frequency in male and female subjects. Bilateral tumors were found in 2 patients (18, 21, 23). Composite adrenal PHEO-GNs are considered as benign in nature. However, only 1 case has been reported with liver metastases at the time of autopsy (21). Our case was disease and symptom free at 6 months, and his hypertension was controlled with antihypertensive therapy.

Most of the composite adrenal PHEO-GNs have been reported to be endocrinologically active. The clinical signs and symptoms of tumor are usually similar to those of pure PHEOs (14, 18). Clinically, active PHEO may produce the classic symptoms of headache, palpitations, and excessive sweating in 50% of the cases. Also, hypertension, either sustained or paroxysmal, is the principal feature of PHEO (3, 12). Composite PHEO-GNs usually secrete excessive catecholamines and their metabolites, and they rarely secrete vasoactive intestinal polypeptide (VIP) (13, 16, 17, 26-28). Rarely, watery diarrhea, hypokalemia and achlorhydria (WDHA) syndrome due to excessive VIP secretion can be observed in patients with composite PHEO-GN. These cases are frequently normotensive because of vasodilatory action of VIP and lack typical symptoms such as headaches (14, 16, 28, 29). Composite adrenal PHEO-GN may be incidentally discovered, manifested as catecholamine-induced acute relapsing pancreatitis without hypertension (19). These composite adrenal tumors may be associated with sporodic tumors or as part of familial tumors such as neurofibromatosis type 1 (NF-1), von Hippel-Lindau disease, MEN 2A and 2B syndromes (14, 17, 18, 20, 21, 30-32). In our case, no features of either NF-1 or MEN or adrenocortical tumor were observed.

On imaging procedures such as CT, MR or ^{18}F-FDG-PET, composite adrenal PHEO-GNs commonly appear as a well-defined, smooth or lobulated heterogeneous mass with varying admixtures of PHEO and GN components (2, 12, 14, 21). However, approximately one third of all cases show a nonspecific appearance that may overlap with the appearance of adrenocortical carcinoma (14, 33). Moreover, imaging procedures are essential for the detection of enlarged lymph nodes or other metastatic foci suggestive of malignancy (34). Also, most of the adrenal carcinomas are larger than 6 cm and typically heterogeneous on CT scan and MR imaging. These features were not observed in our case. Hovewer,

benign and malignant oncocytic neoplasms cannot be differentiated on the basis of the imaging characteristics.

Grossly, composite adrenal PHEO-GNs usually resemble typical PHEOs. Therefore, mixed phenotype is generally detected by a pathologist (18). The PHEO component of the tumor was reddish-tan with a hemorrhagic appearance whereas the GN component of the tumor was whitish-yellow in the cut surface (21). In both macroscopic and microscopic examination, PHEO is usually the predominant component as was seen in the present case.

The histogenesis of composite adrenal PHEO-GNs has been attributed to the common embryologic origin of the chromaffin and neural cells from the neural crest (14, 15, 35). Therefore, microscopically, these tumors are composed of chromaffin cells and the sympathetic ganglion cells (14). The presence of stromal properties may be a clue to a mixed phenotype (18). The tumors may be traversed by bundles of spindle cells that can be shown immunohistochemically to contain Schwann cells and axons, or there may be patchy areas with unusually prominent sustentacular cells (18). In immunochemical analysis, PHEO component of these tumors is usually strongly positive for chromogranin A, and the GN component is negative chromogranin A, but frequently positive for S-100 protein, neurofilament antibody and neuron-specific enolase (13-15, 18). In our patient, the immunohistochemical profile was typical for composite adrenal PHEO-GN.

The definitive treatment of choice for composite adrenal PHEO-GN is complete surgical resection when possible (4, 12-18). With the development of laparoscopic technique, adrenal tumor can be removed under laparoscopic procedure (34). The acute and chronic effects of increased plasma catecholamines should be reversed prior to the surgical excision of the tumor. Combined α-and β-adrenergic blockades are required preoperatively to control high blood pressure and to prevent intraoperative hypertensive crises (36). An α-adrenergic blockade (e.g., phenoxybenzamine or doxazosin) should be started at least 7 days preoperatively to allow for expansion of the contracted blood volume. A liberal salt diet is advised during the preoperative period. Once adequate α-adrenergic blockade is achieved, β-adrenergic blockade (e.g., propranolol or labetalol) is initiated (e.g., at least 3 days preoperatively). The differential diagnosis of these tumors would include other adrenal tumors such as adrenocortical adenoma or carcinoma, and pure PHEO (4). Hence, a thorough pathological examination is essential to delineate the components of this tumor (4). Prognosis of completely resected composite adrenal PHEO-GNs is excellent without further therapies (4, 13, 17, 18, 21). The recurrence rate for composite adrenal PHEO-GN is near zero. However, distant metastasis and familial syndromes associated with these tumors have been reported (21). Therefore, composite adrenal PHEO-GNs should be surgically excised completely and should be followed for a long period after the operation. In addition, life-long clinical and biochemical follow-up of

patients with adrenal composite PHEO-GN is essential.

In conclusion, composite adrenal PHEO-GN is a rare entity and preoperative diagnosis is fairly difficult. Its hormonal activity and imaging characteristics are frequently very similar to those of other adrenal tumors, especially pure PHEO and adrenal carcinoma. Therefore, careful evaluation by endocrine tests and multiple imaging procedures are required for a differential diagnosis. However, definitive diagnosis composite adrenal PHEO-GN is established by histological and immunochemical studies.

Conflict of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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