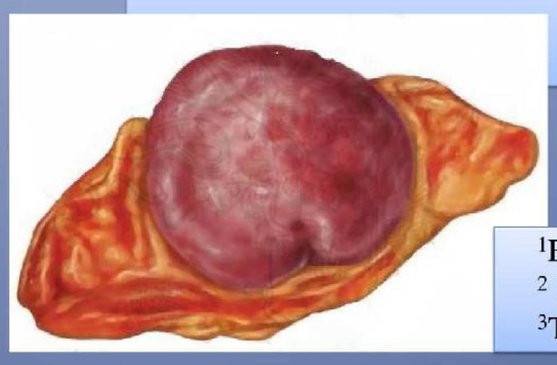
Adrenocorticotropic hormone-producing pheochromocytoma
4 cases report



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INTRODUCTION

Ectopic secretion of ACTH from non-pituitary tumors, referred to as ectopic ACTH syndrome (EAS), accounts for about 10-20% of Cushing's syndrome (CS). Cushing syndrome may be due to ectopic secretion of adrenocorticotrophic hormone (ACTH) from bronchial carcinoid, islet cell tumor, small cell lung carcinoma, medullary carcinoma of the thyroid, thymic carcinoid, disseminated neuroendocrine tumors and disseminated gastrointestinal carcinoid.

Ectopic hormone-secreting pheochromocytomas (Pheo) are rare. Since 1955, when Roux published the first association between pheochromocytoma and Cushing's syndrome. Pheochromocytoma represents a rare cause of hypercortisolism, accounting for less than 5% of ectopic Cushing's syndrome while less than 1% of pheochromocytomas is accompanied by Cushing's syndrome

We are reporting about 4 cases of ACTH-secreting pheochromocytoma presenting as Cushing's syndrome.

CASE REPORT

Data from 4 patients were analysed. There were 4 women from 50 to 63 years old. All patients had a clinical presentation of hypercorticoidism: dysplastic obesity, hypertension, hypokalemia, systemic osteoporosis (Tabl.1). Their levels of adrenocorticotropic hormone in plasma, 24-hour urinary free cortisol and urinary catecholamine were high (Tabl.2).

TABLE 1. Clinical signs and symptoms of patients with ACTH-secreting pheochromocytomas

Patients Sex /Age	Time from first symptoms to setting diagnoses	The most characteristic clinical signs and symptoms of		
		pheochromocytoma	*EAS*	
G. F/64	5 years	○ Hypertension ○ Tachycardia ○ Body weight increase	• Hyperpigmentation • Diabetes mellitus • Muscle weakness • Osteopenia or osteoporosis • Hypokalemia • Moon facies • Truncal obesity, buffalo hump, supraclavicular fat pad • Hypertension	
A. F/58	6 months	○ Hypertension		
B. F/50	1 year	○ Hypertension ○ Body weight increase		• secondary immunodeficiency
M. F/53	2 years	○ Hypertension		

TABLE 2. The main laboratory findings of patients with ACTH-secreting pheochromocytomas

Patients Sex /Age	Hormonal characteristics				
	ACTH, pg/ml 8.00/23.00 [7,0-66,0]/ [0-30,0]	**Plasma cortisol,** *nmol/L 8.00/23.00 [123,0-626,0]/ [46,0-270,0]*	**Total 24-h urinary cortisol,** nmol/24h *[60,0-413,0]*	**Metanephrine,** mg/24h *[25-312]*	**Normetanephrine** mg/24h *[35-445]*
G. F/64	189/211	962/1256	960	1553	640
A. F/58	There is no reliable data	4655/2460	3726	There is no reliable data	There is no reliable data
B. F/50	178,7/179,8	1488/1672	9596	1481	830
M. F/53	176,1/281	1750/1626	3828	638	545,6

Computed tomography scan of the abdomen in all cases revealed a mass in the left adrenal gland (Tabl.3, Fig.1).

The results of hormonal analysis and imaging study clearly established the left adrenal gland as the source of ACTH overproduction. Left sided adrenalectomy was performed under treatment with a-blocker doxazosin and b-blocker atenolol. Histological examination revealed in 3 cases – pheocromocytoma and in 1 case corticomedullary mixed tumor of the adrenal gland (Tabl.3, Fig.2). Mixed corticomedullary tumors are extremely rare and present as a single tumor mass composed of an intimately admixed population of both adrenal cortical cells and pheochromocytes.

Additional immunostaining (IHC) of these tumors showed positive immunostaining for chromogranin, s-100 protein and ACTH. The IHC research for somatostatin receptors of subtype 2 and 5 (SSTR2, SSTR5) was performed in 3 cases and showed predominately expression SSTR2. In this case index of Ki-67 was not high, from 0,5 to 4% (Tabl.3, Fig.2).

Clinical and biochemical signs of hypercortisolism rapidly began to rapidly disappear after surgery. Follow up of the patients during the next 2 years on average was with disease remission.

TABLE 3. Topic diagnosis and pathology report of patients with ACTH-secreting pheochromocytomas

Patients Sex /Age	Computed tomography scan	Histological examination	immunostaining
G.. F/64	2 ovoid formations of the left adrenal gland 18x23x25 mm (density 19 HU) and 20x23x25 mm (density 3 HU)	corticomedullary mixed tumor with diffuse-nodular hyperplasia of the adrenal cortex	ACTH «+» CRH «-» The index of Ki67 = 2,5% SSTR2- not examine SSTR5- not examine
A.. F/58	ovoid mass of 20x16 mm in the left adrenal gland (density 27 HU)	pheocromocytoma with diffuse hyperplasia of the adrenal cortex	ACTH «+» CRH «-» The index of Ki67 =0,5% SSTR2«+» SSTR5«-»
B.. F/50	rounded mass of 27x30x46 mm in the left adrenal gland (density 19 HU)	pheocromocytoma	ACTH «+» CRH «-» The index of Ki67 = 4% SSTR2«+» SSTR5«-»
M.. F/53	mass with cysts d.43 mm in the left adrenal gland	pheocromocytoma with diffuse hyperplasia of the adrenal cortex	ACTH «+» CRH «-» The index of Ki67 =3% SSTR2«+» SSTR5«+»

ACTH - adrenocorticotropic hormone; CRH- corticotropin releasing hormone; PCCT 2 – somatostatine receptors 2 и 5 subtype .

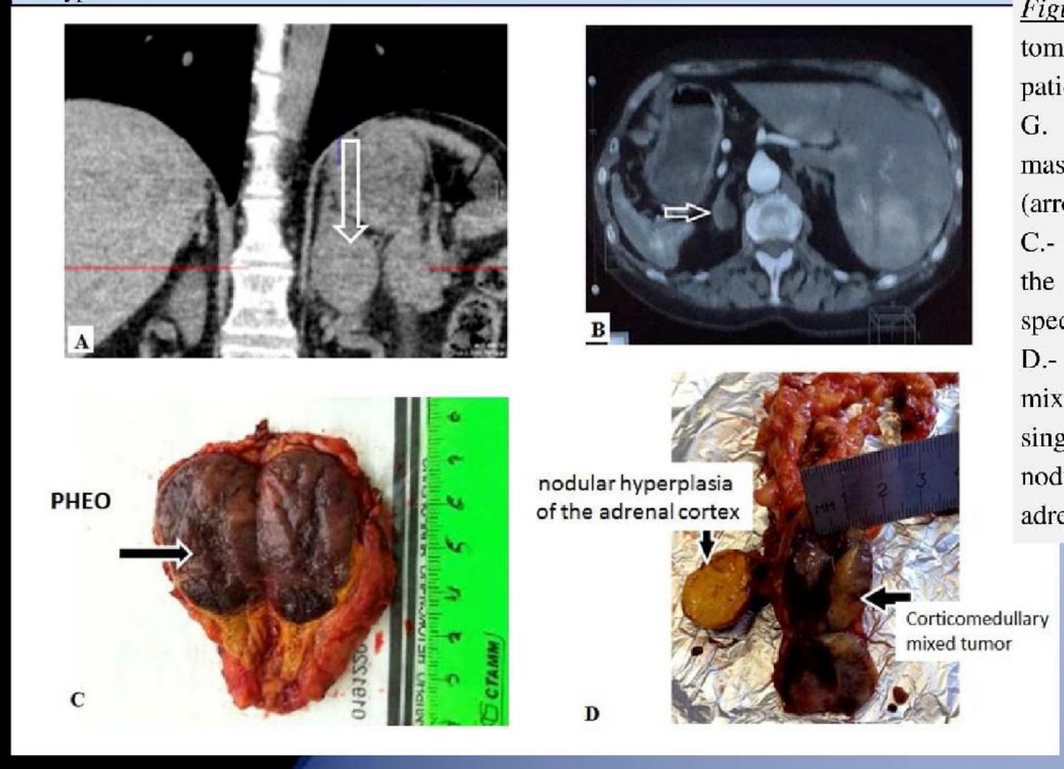

Figure 1. Computed tomography scan of the patient B. (A.) and patient G. (B.) showing large masses in the left adrenal (arrows);
C.- Gross appearance of the pheochromocytoma specimen (patient A.)
D.- Corticomedullary mixed tumor present as a single tumor mass with nodular hyperplasia of the adrenal cortex (patient G.)

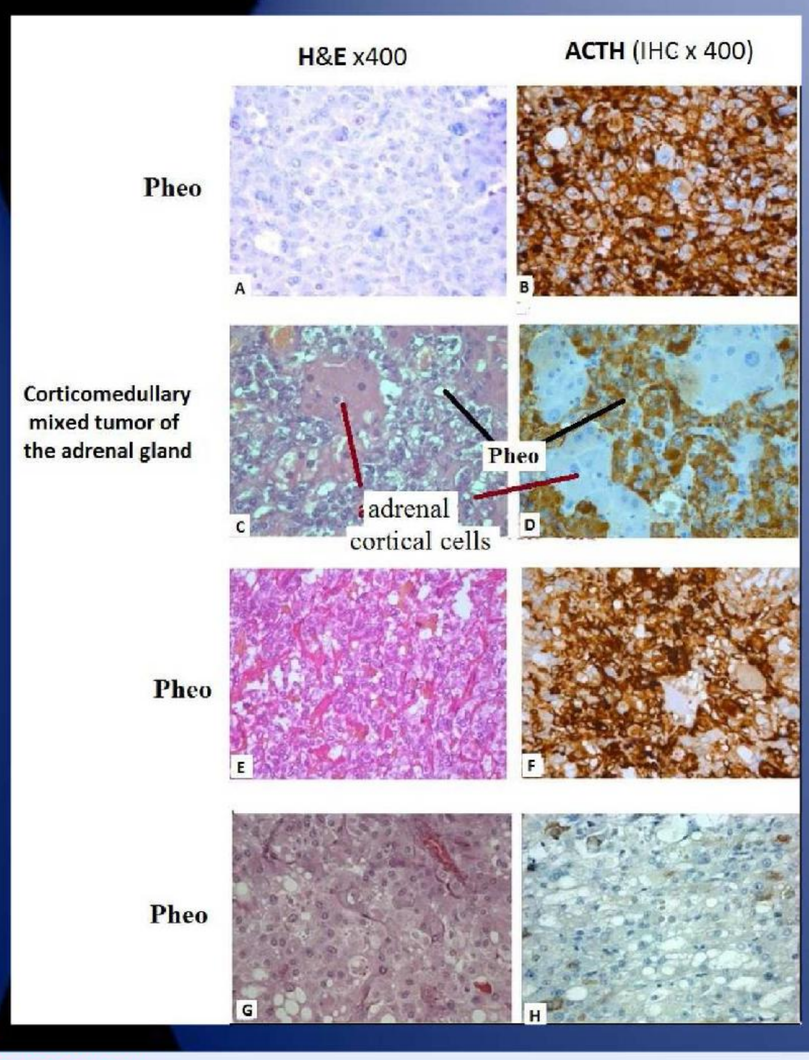

Figure 2. Microscopically:
Patient A. A - histopathology showing tumor cells of pheochromocytoma (H&E x 400), B – Intense immunoreactivity for ACTH (x 400);
Patient G. C. – Mixed corticomedullary tumors composed of an intimately admixed population of both adrenal cortical cells and pheochromocytes (H&E x 400), D –histochemically pheochromocytes showed positive saining for ACTH (x 400);
Patient M. E- pheochromocytoma: the trabecular arrangement (Zellballen) of neoplastic chief cells with abundant cytoplasm (H&E x 400), F. – tumor cells showing diffuse strong positive immunoreactivity with ACTH (x 400);
Patient B. G - pheochromocytoma: nests and sheets of amphophilic polygonal cells (H&E x 400), H – immunoreactivity for ACTH in a single cells of the pheochromocytoma (x 400).

CONCLUSION

Cushing syndrome can be a rare presentation of pheochromocytoma as a result of ectopic secretion of ACTH. It is often difficult to diagnose this presentation preoperatively, especially in cases with a predominant secretion of ACTH rather than catecholamines. In such cases, the final diagnosis can be made only by immunohistochemical analysis.

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