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Ectopic ACTH Syndrome Due to Pheochromocytoma: Case Report and Review of the Literature

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A 51-year-old female was diagnosed preoperatively to have a pheochromocytoma producing ACTH. This diagnosis was based upon her paroxysmal hypertension, hyperpigmentation, and hypokalemia. Elevated levels of serum and urine corticosteroids, plasma ACTH, urinary VMA, and catecholamines fell after a right adrenal pheochromocytoma was removed. Subsequently this tumor was found to have a high content of ACTH. Review of the literature indicates a mortality rate of 57% for this syndrome. Proper preoperative recognition and management can result in total cure.

The syndrome of ectopic production of ACTH, in which a corticotrophin-like substance is produced by non-pituitary neoplasms may occur with various types of tumors [1,2]. Most cases fall into one of four general categories: (1) oat cell bronchial carcinoma, (2) endocrine tumors of foregut-derived tissue, (3) ovarian tumors, and (4) pheochromocytoma and related tumors [3]. In the present report we describe a patient with an ACTH-producing pheochromocytoma and review the literature on chromaffin tumors associated with hypercortisolism.

CASE REPORT

A 51-year-old white female was admitted to the Yale-New Haven Hospital with hypertension, hyperpigmentation, weight loss, and emotional lability. She was well until five months prior to admission, when she sought medical attention because of anxiety. Her blood pressure at that time was 130/80 mm Hg. Serum thyroxine was normal. In the ensuing three months, she developed what she described as a "cortisone face," having remembered her appearance after receiving cortisone for a nine-month period 22 years prior to admission as experimental therapy for Rh incompatibility. She also noted a change in body habitus with central redistribution of body fat, although she was not obese, and had lost ten pounds of weight. She developed ankle edema, easy bruising, poor healing of wounds, increased facial and body hair, facial acne, proximal muscle weakness, generalized increased skin

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pigmentation despite minimal sun exposure, marked emotional lability, fine, thin skin, and the cessation of previously regular menses. She also complained of repeated episodes of tremulousness, profuse sweating, and headaches. Five weeks prior to admission, she began to take a thiazide diuretic with KCl supplement as therapy for hypertension. These medications were discontinued one week prior to admission and at the time of hospitalization the only medication was ferrous sulfate. She had smoked one pack of cigarettes a day for 35 years. There was no family history of endocrine disease; several members of the family had prominent eyes but were euthyroid.

On physical examination, the patient appeared anxious and had "moon facies." The blood pressure was 170/110 mm Hg in both arms supine and sitting, respiratory rate 17, the pulse 120 and regular, and the temperature was 98° F. The skin was thin and smooth with diffusely increased pigmentation, numerous ecchymoses and petechiae. She also had fine facial hair. There were no hyperpigmented scars or purple striae. She had bilaterally prominent eyes without proptosis or lid lag. Funduscopic examination was normal as were fields of vision by confrontation. The thyroid gland was normal. There was no prominence of the supraclavicular or dorsocervical fat pads nor any lymphadenopathy. The heart and lungs were normal. The vertical span of the liver was 13 cm in the right midclavicular line and there were no abdominal masses. Rectal, pelvic, and neurological examinations were normal. She had 1+ pretibial edema.

The hematocrit was 47% and the white cell count 19,000 with 91% neutrophils, 2% band forms, 2% lymphocytes, and 5% monocytes. Platelet count was 420,000. Serum sodium was 147 mEq/L, potassium 2.2 MEq/L, bicarbonate 39 mEq/L, and chloride 91 mEq/L. The BUN was 23 mg/dl and the creatinine was 1.1 mg/dl. Random serum glucoses varied between 105 and 170 mg/dl. Total serum calcium was 11.3 mg/dl and phosphate 2.8 mg/dl. Two days later, after the discontinuation of all medication, repeat values were 10.4 mg/dl and 3.3 mg/dl, respectively. The serum albumin was 3 g/dl, a 24 hour urine sample contained 1.3 g of protein. Serum calcitonin [4], prolactin [5], and parathyroid hormone [6] were normal. Routine chest x-ray, full lung tomograms, sella turcica films, and formal fields of vision by Goldmann perimetry were normal. Electrocardiogram was normal; there were no premature beats. The serum thyroxine was 3.2 micrograms/dl (normal range 4.6–9.2), and the estimated free thyroxine 0.5 mcg/dl (normal range 1.0–2.1). Serum TSH was undetectable. I-131 uptake was 7% and diffusely decreased. Total blood volume was normal [7]. Pertinent hormone studies are shown in Table 1.

An abdominal ultrasound examination (Fig. 1) identified a right cystic adrenal mass and subsequent abdominal "CAT" scan (Fig. 2) confirmed the right adrenal mass and demonstrated left adrenal enlargement. Abdominal aortic angiography characterized the right adrenal mass as cystic (Fig. 3). Blood pressure rose briefly to 260/140 mm Hg during this study. Other endocrine neoplasia were not present based on the normal sella films, calcitonin, parathyroid hormone, serum glucose levels, and thyroid scan. Serum calcium became normal after thiazide diuretic therapy was discontinued.

The data presented in Table 1 indicated hyperfunctioning of both the adrenal cortex and medulla. The clinical diagnosis was consequently ectopic ACTH syndrome due to a pheochromocytoma. Therefore, preoperative management consisted of spironolactone administration to correct the hypokalemia and lower the pressure along with phenoxybenzamine as specific antihypertensive therapy for the presumed

TABLE 1

	Baseline	Day 3 Low Dose Dex	Day 2 High Dose Dex	Post-Op	Normal Values
Cortisol					
8 AM	135	125	164		12-25 mcg/dl
8 PM	75				less than 12 mcg/dl
Urine 17 OH	88.4	80.3	16		3-10 mg/24 hr
Urine 17 KS	53.3	48.2	47.9		5-15 mg/24 hr
ACTH [8]					
8 AM	180			<10	10-80 pg/ml
8 PM	226				
V.M.A. [9]	33				<5 mg/24 hr
Norepinephrine	215			11.2 (total)	0-100 mcg/24 hr calculated as nor-
Epinephrine [10]	112				epinephrine.
Renin [11]	2.5				0.6-4.6 ng/ml/hr

pheochromocytoma. Oral liothyronine therapy was begun to ensure euthyroid status. Sympathetic blocking drugs as well as pressor agents were "on standby" during surgery and an arterial line and Swan-Ganz catheter were placed preoperatively.

On the ninth hospital day the right adrenal tumor was removed. Blood pressure fell to normal as soon as the right adrenal vein was ligated. Palpation of the left adrenal gland revealed a small firm mass, and therefore the left adrenal gland was also removed.

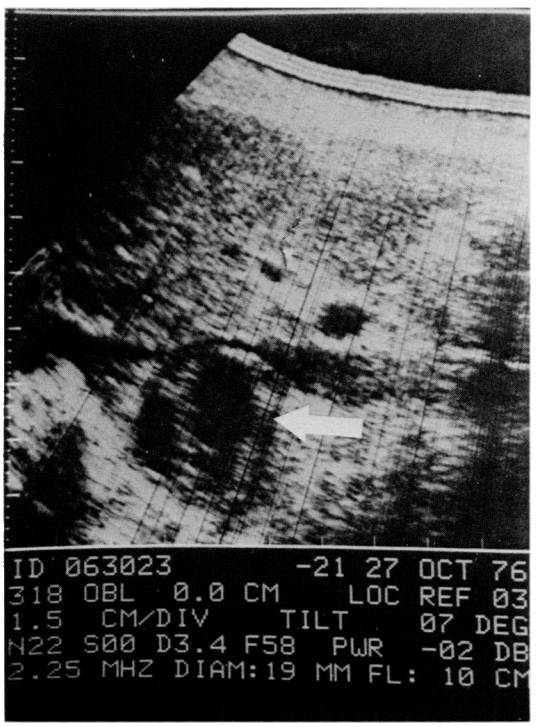

FIG. 1. Abdominal ultrasound showing a 3 to 4 cm cystic mass (*arrow*) in the region of the right adrenal gland.

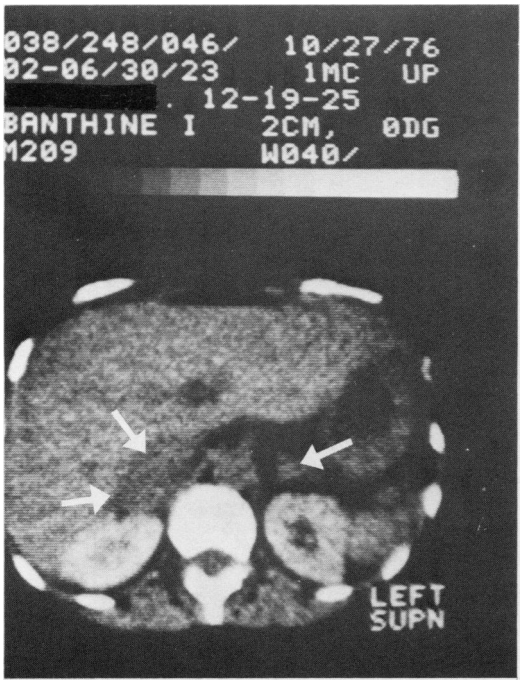

FIG. 2. Computerized Axial Tomogram, transaxial view, showing a large right adrenal mass (*double arrows*) and a slightly enlarged left adrenal gland (*single arrow*).

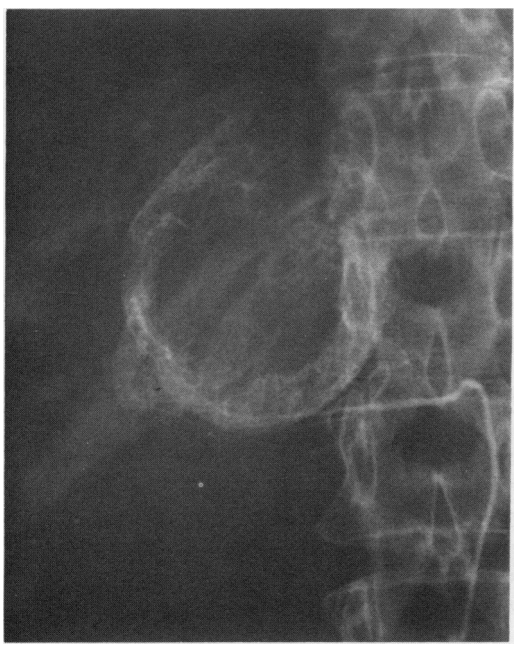

FIG. 3. Arteriogram-delayed film after selective right middle adrenal artery injection. The cystic nature of the tumor is apparent.

PATHOLOGY

The right adrenal (Fig. 4, top) weighed 100 grams and included a partly cystic gray-brown mass, 8 × 5 cm in cross section containing approximately 40 cc of hemorrhagic fluid within the cystic space. This mass was an encapsulated medullary tumor showing the typical light microscopic features of a pheochromocytoma (Fig. 5). Thin section electron microscopy showed membrane-bound osmiophilic granules of two types: some were filled with electron-dense material and others showed a clear halo, corresponding to epinephrine- and norepinephrine-containing granules, respectively [12] (see Fig. 6).

The contralateral adrenal (Fig. 4, bottom) weighed 22 grams and was generally thickened, with a grossly evident 1 cm zone of poorly demarcated hyperplasia. This lesion, which consisted mostly of clear cells but also some compact cells and necrotic foci, merged at its periphery with diffusely hyperplastic adrenal cortex. The residual medullary tissue was normal in appearance.

Cystic fluid was assayed for ACTH by BioScience Laboratories [8] and was reported to contain over 10 ng/ml. This fluid was also assayed for ACTH activity by Dr. David Orth at Vanderbilt University School of Medicine, and was found to contain over 17.5 ng/ml [13]. Tissue assay for ACTH was also kindly performed by Dr. Orth and was 180 ng/g wet tissue [14]. Plasma ACTH levels 2 days postoperatively were less than 10 pg/ml.

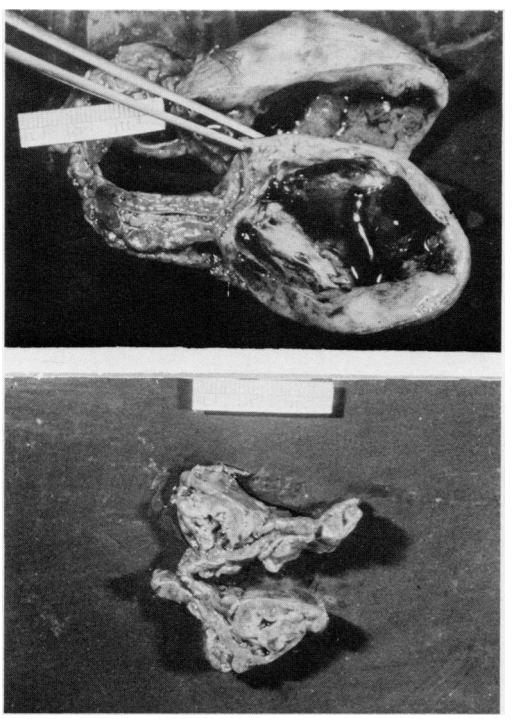

FIG. 4. The right adrenal gland (*top*) with the cystic pheochromocytoma. Note the thickened adrenal cortex. The left adrenal (*bottom*) was enlarged with nodular hyperplasia of the cortex.

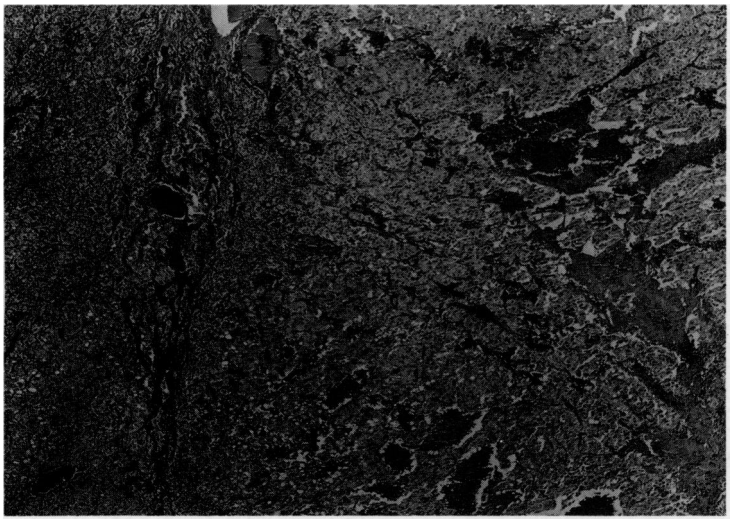

FIG. 5. Photomicrograph illustrating the pheochromocytoma. Nests of ovoid and spindle cells are separated by vascular channels. Note laking of blood (*right*). (× 125)

LITERATURE REVIEW

In 1964 Bourgoignie et al. [15] reported a case of pheochromocytoma associated with Cushing's syndrome and hyperaldosteronism. Their review of previous case reports revealed eleven cases of adrenocortical hyperplasia or adenomata in patients with chromaffin tumors. Medullary pheochromocytomas were associated with cortical hyperplasia in four cases [16–19] and with both hyperplasia and adenomata in two cases [20,21]. Two patients had a chemodectoma, a medullary pheochromocytoma, and an adrenocortical adenoma [22,23]. The literature prior to 1964 also

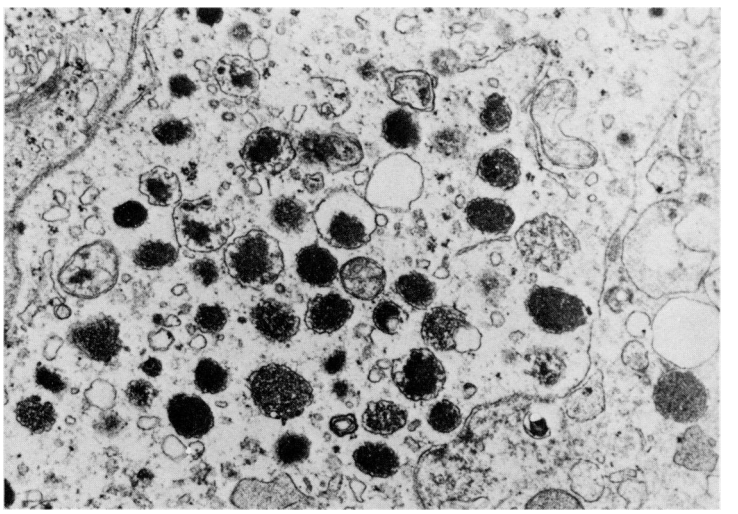

FIG. 6. Electron micrograph of tumor cells demonstrating two types of neurosecretory granules resembling both epinephrine and norepinephrine containing vesicles (see text). (× 28,000).

includes two additional patients [24–26] and since Bourgoignie's review, there have been sixteen case reports of chromaffin tumors associated with hypercortisolism or hyperplasia of the adrenal cortex. Of these, four are too brief to permit adequate assessment [27,28], and three other cases are probably not due to ACTH production by the chromaffin tumors, despite the presence of hypercortisolism [29–31]. In particular, Mathison and Waterhouse [29] reported a case of Cushing's syndrome secondary to a mixed cortico-medullary tumor in which corticosteroid production by the tumor appears a more likely etiology than ectopic ACTH production. Medullary thyroid carcinoma coexisted with a pheochromocytoma and adrenocortical hyperplasia in the case of Mathys et al. [30], so that idiopathic Cushing's disease or production of ACTH by either tumor are plausible etiologies for the patient's hypercortisolism. A selective mineralocorticoid excess was observed by Wilson et al. [31] but had there been ectopic ACTH production, elevated glucocorticoid levels would also have been expected.

Three other cases are equivocal, although consistent with ectopic ACTH production by a pheochromocytoma. However, Bucalossi et al. [32] report no ACTH levels in their unique case of a mediastinal pheochromocytoma associated with signs of hypercortisolism. The cases of Rambert et al. [33] and Gerasimenko et al. [34] are also consistent clinically with the ectopic ACTH syndrome, but these authors reported normal plasma ACTH levels (on isolated random samples) and no ACTH determinations were made on the tumor tissue.

By itself the presence of tissue ACTH is not sufficient to establish a diagnosis of ectopic ACTH syndrome in view of Liddle's findings of demonstrable ACTH activity in tumor tissue extracts in 8% of patients without the ectopic ACTH syndrome [25]. For conclusive proof, five criteria should be satisfied: (1) clinical and laboratory evidence of hypercortisolism should be present; (2) ACTH activity should be present in tumor extracts; (3) plasma ACTH should be clearly elevated; (4) elevated ACTH levels should be evident in the venous effluent from the tumor site; (5) ACTH activity should fall after removal of the tumor. The case of Schteingart et al. [35] fulfilled the first four of these criteria. Bourgoignie [15] and Meloni et al. [36] established elevated tumor, but not plasma, ACTH levels in their cases. Both tissue and plasma ACTH activities were reported in the cases of O'Neal et al. [26], Burmeister and Simon [37], Berenyi et al. [38] as well as in the present case.

Several generalizations can be made after examination of these seven cases with well documented ectopic production of ACTH. All of the patients were women, with ages ranging from 26 to 67 years (mean 46) at diagnosis; all had unilateral nonmetastatic adrenal medullary tumors, two of which were classified as paragangliomas [35,36]. Two had a slow indolent course more typical of idiopathic Cushing's syndrome [26,37], whereas the remaining five had a clinical presentation most compatible with ectopic ACTH production (marked weakness and disorientation, hyperpigmentation and weight loss, with a rapid course). Four of the five patients with the histologic diagnosis of pheochromocytoma had exhibited paroxysmal hypertension.

Despite the apparent curability of this syndrome, since all the reported tumors were nonmetastatic, the survival rate was only 43 percent. Three patients died of surgical complications and another of pneumonitis before surgery was attempted. The three patients who survived surgery, including the present case, have apparently been cured. Our patient is alive and well 2½ years after surgery requiring only cortisone acetate 37½ mg per day.

DISCUSSION

The present case raises many points of clinical and theoretical interest. Unlike most previously reported cases, the diagnosis of ectopic ACTH production by a pheochromocytoma was made preoperatively. Therefore the serious consequences of misdiagnosis, improper preoperatrive management, and postoperative complications were averted. Ectopic ACTH production was suspected by the triad of hypertension, hyperpigmentation, and hypokalemia. A pheochromocytoma was suspected because of paroxysmal hypertension and proven by the VMA and catecholamine studies. Another possibility considered was a mixed cortico-medullary tumor similar to the one reported by Mathison and Waterhouse [29]. However, the presence of hyperpigmentation led us to favor the ectopic ACTH diagnosis.

The reduced thyroid function tests observed preoperatively in our case are attributable to the known suppressive effects of elevated corticosteroids on thyroid function [39]. Circulating thyroxine, TSH, and I-131 uptake, which were low preoperatively, normalized after surgery. Epinephrine production increases after corticosteroid administration, presumably due to the induction by glucocorticoids of phenylethanolamine-N-methyltransferase (PNMT), the enzyme which converts norepinephrine to epinephrine [40]. In the present case, urinary excretion of epinephrine was elevated and epinephrine-containing secretory granules were seen on electron microscopy (Fig. 6). However, direct tumor tissue assay for PNMT, kindly performed by Dr. Linda Hegstrand, showed minimal activity [41,42]. The exact explanation for these findings is unclear.

Despite the good prognosis in the majority of uncomplicated pheochromocytomas, our review of the literature indicates an inordinately high morbidity and mortality in those that produce ACTH. Despite the rarity of this syndrome, all patients with Cushing's syndrome should be screened for catecholamine excess. Preoperative recognition of the presence of a pheochromocytoma in a patient with clinical features of Cushing's syndrome is essential for effective management and cure of this syndrome.

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