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EXTENSIVE CLINICAL EXPERIENCE

Cushing's Syndrome Due to Ectopic Corticotropin Secretion: Twenty Years' Experience at the National Institutes of Health

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Context: Ectopic ACTH secretion (EAS) is difficult to diagnose and treat. We present our experience with EAS from 1983 to 2004.

Setting: The study was performed at a tertiary care clinical research center.

Patients: Ninety patients, aged 8–72 yr, including 48 females were included in the study.

Interventions and Outcome Measures: Tests included 8 mg dexamethasone suppression, CRH stimulation, inferior petrosal sinus sampling (IPSS), computed tomography, octreotide scan, magnetic resonance imaging, and/or venous sampling. Therapies, pathological examinations, and survival were noted.

Results: Eighty-six to 94% of patients did not respond to CRH or dexamethasone suppression, whereas 66 of 67 had negative IPSS. To control hypercortisolism, 62 patients received medical treatment, and 33 had bilateral adrenalectomy. Imaging localized tumors in 67 of 90 patients. Surgery confirmed an ACTH-secreting tumor in 59 of 66 patients and cured 65%. Nonthymic carcinoids took longest to localize. Deaths included three of 35 with pulmonary carcinoid, two of five with thymic carcinoid, four of six with gastrinoma, two of 13 with neuroendocrine tumor, two of two with medullary thyroid cancer, one of five with pheochromocytoma, three of three with small-cell lung cancer, and two of 17 with occult tumor. Patients with other carcinoids and ethesioneuroblastoma are alive.

Conclusions: IPSS best identifies EAS. Initial failed localization is common and suggests pulmonary carcinoid. Although only 47% achieved cure, survival is good except in patients with small-cell lung cancer, medullary thyroid cancer, and gastrinoma. ***(J Clin Endocrinol Metab* 90: 4955–4962, 2005)**

ECTOPIC SECRETION OF ACTH from a nonpituitary tumor causes approximately 10% of Cushing's syndrome (CS) (1–5). When Liddle first codified the syndrome as ectopic secretion of ACTH (EAS), most patients presented with small-cell lung cancer (6). In the ensuing 40 yr, the spectrum of causes broadened to include other, more occult tumors (7–10).

EAS presents throughout the life span with variable features including psychiatric, infectious, orthopedic, reproductive, and nonspecific systemic complaints. As a result, patients may present to clinicians of many specialties, and recognition of the disorder may be delayed. Subsequently, it may be difficult to locate the ACTH source and manage the patients' hypercortisolism.

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Abbreviations: CS, Cushing's syndrome; CT, computed tomography; EAS, ectopic secretion of ACTH; HDDST, high-dose dexamethasone suppression test; 5-HIAA, 5 hydroxyindoleacetic acid; IPSS, inferior petrosal sinus sampling; MRI, magnetic resonance imaging; 17OHCS, 17-hydroxycorticosteroid excretion; O/N DST, overnight high-dose dexamethasone suppression test; TSS, transsphenoidal pituitary surgery; UFC, urine cortisol.

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The aim of this study was to present our experience with EAS at the National Institutes of Health (NIH) during 20 yr to assist practitioners with the difficulties in diagnosis and management of this disorder.

Patients and Methods

Patients

We retrospectively reviewed the records of patients with EAS admitted to the NIH Clinical Center from 1983 through 2004. The records were completed by endocrinology residents and attending physicians. Patients participated in protocols approved by the Investigational Review Board of the National Institute of Child Health and Human Development and gave written informed consent. Some patients were reported previously in studies focused on diagnosis (11–21), presentation (22, 23), or treatment (24–26).

Diagnostic evaluation

We measured morning electrolytes, glucose, serum cortisol, and plasma ACTH levels; 24-h urine cortisol (UFC) and/or 17-hydroxycorticosteroid excretion (17OHCS); and/or midnight plasma cortisol concentration. Depending on the attending physician, patients underwent an 8-mg 2-d high-dose dexamethasone suppression test (HDDST) (15), 8-mg overnight high-dose dexamethasone suppression test (O/N DST) (27), ovine CRH stimulation test (28), and/or inferior petrosal sinus sampling (IPSS) before and after the administration of CRH (17), all of which were performed and interpreted as previously described.

After a provisional diagnosis of EAS was assigned, tests were ob-

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tained to identify the source of ACTH. These included markers of tumors that secrete ACTH, including urine 5-hydroxyindoleacetic acid (5-HIAA), and serum gastrin or calcitonin. Urine catecholamines and metabolites were measured in hypertensive patients. Imaging studies included computed tomography (CT) and/or T1- and T2-weighted magnetic resonance imaging (MRI) scans of the neck, chest, and/or abdomen/pelvis. Occasionally patients underwent scintigraphy with 6 mCi (222 MBq) and/or 18 mCi (666 mBq) (21) of [^{111}In]DTPA-D-Phe-pentetreotide (octreotide) or 0.5 mCi (19.5 MBq) [^{131}I]-metaiodobenzylguanidine. Usually imaging was repeated every 6 months for 1–2 yr and then every 1–2 yr. Some patients had bone mineral density measured and/or underwent selective venous catheterization and sampling for ACTH measurements.

Assays

A previously described RIA (29) or an immunoradiometric assay (Nichols Institute Diagnostics, San Clemente, CA) was used to measure ACTH. RIA and immunochemiluminometric assays were used for measurement of plasma and urine cortisol. These assays had similar characteristics and normal ranges (30, 31). Urinary 17OHCS was measured using a modified colorimetric method (32). Commercial assays were used to measure calcitonin and gastrin. Catecholamines were measured by radioenzymatic assay; 5-HIAA, vanilylmandelic acid, and metanephrines were measured with high-performance liquid chromatography.

Analysis

Patients received a provisional diagnosis of EAS based on IPSS results. When IPSS was not available, the provisional diagnosis of EAS was based on responses to CRH and dexamethasone tests or pathology results. The final diagnosis was based on surgical cure and/or pathological examination (including ACTH immunohistochemistry) of tumor. Those patients in whom a tumor was not identified at the most recent evaluation were considered to have occult ectopic ACTH secretion. Patients were considered cured if postoperative cortisol values were less than 5 μg/dl. Comparisons of biochemical findings and dynamic testing between patients with known ectopic ACTH-secreting tumors and patients with presumed ectopic ACTH-secreting tumors (occult/unknown) were done with Wilcoxon's test and the χ^2 test with Yates' correction, respectively (by I.I.); statistical significance was set at $P < 0.05$. Two investigators (R.A.W. and I.I.) performed survival analysis and comparisons using the Kaplan-Meier method and the Cox-Mantel test, respectively. Two investigators (I.I. and L.K.N.) reviewed the entire data set and results.

Results

Patients

Forty-two males and 48 females (76 white, six Hispanic, and eight African-American) were diagnosed with CS at a mean age ± SD of 37.6 ± 14.8 yr (range 8–72 yr) and diagnosed with EAS about 1 yr later. At presentation the mean body mass index ± SD was 29.7 ± 8.1 kg/m^2 (range 16.0–54.9 kg/m^2). Two patients had multiple endocrine neoplasia 2 syndrome. Table 1 lists the patients' clinical signs and symptoms. Of note, 50% had osteoporosis or fracture. Infections involved the skin (n = 18), urogenital tract (n = 18), wounds (n = 2), upper respiratory tract (n = 6), and peritoneum (n = 1); some patients had multiple infections. Identified agents included opportunistic organisms (n = 7), candida (n = 17), and herpes zoster (n = 4) (some of these data were previously reported in Ref. 22). Forty-eight patients had dysthymia (n = 7), bipolar disorder (n = 1), psychosis (n = 11), panic disorder (n = 1), depression (n = 24), or more than one psychiatric diagnosis (n = 4).

TABLE 1. Clinical signs and symptoms of patients with CS caused by known or presumed ectopic ACTH secretion (n = 90)

	n (%)
Muscle weakness	74/90 (82)
Body weight	
Increase	64/90 (70)
Decrease	9/90 (10)
Hypertension	70/90 (78)
Menstrual irregularities or amenorrhea	28/36 (78)
Hirsutism	36/48 (75)
Osteopenia or osteoporosis[a]	27/36 (75)
Hypokalemia	64/90 (71)
Psychiatric disorders	48/90 (53)
Bruising	47/90 (52)
Infections	46/90 (51)
Diabetes	45/90 (50)
Violaceous striae	40/90 (44)
Truncal obesity	35/90 (39)
Edema	34/90 (38)
Body mass index > 28 kg/m^2	32/90 (36)
Fractures[b]	27/90 (30)
Insomnia	26/90 (29)
Libido	
Decrease	21/88 (24)
Increase	1/88 (1)
Impaired cognition or memory	20/90 (22)
Hyperpigmentation	17/90 (19)

[a] Assessed with dual-photon absorptiometry or dual-energy x-ray absorptiometry.

[b] Assessed with x-rays; in some patients fractures were noted in more than one location; 14 had vertebral fractures/compression, six had fractures in the lower and three in the upper limbs, and 10 had rib fractures.

Previous treatment

Twenty patients had one or more previous operations, including thoracotomies for biopsy (n = 1) or resection of thymic (n = 1) or pulmonary carcinoids (n = 2), transsphenoidal pituitary surgery (TSS) (n = 13), unilateral adrenalectomy (n = 3), or bilateral adrenalectomy to control hypercortisolemia (n = 5). One patient received pituitary radiotherapy after TSS.

Forty-five patients received diet (n = 20), oral hypoglycemics (n = 7), or insulin (n = 18) therapy for diabetes mellitus. Thirty-nine received potassium or potassium-sparing diuretics. Thirty-six patients discontinued steroidogenesis inhibitors 4–6 wk before admission.

Biochemical findings

All patients but two with periodic CS had increased UFC (mean, 3,379 μg per 24 h; range, 59–35,000 μg per 24 h; mean, 9,326 nmol per 24 h; range, 162–96,250 nmol per 24 h; normal ranges in Table 2) and/or 17OHCS (mean, 51.3 mg per 24 h; range, 1.8–193.5 mg per 24 h; mean, 142 μmol per 24 h; range, 5–534 μmol per 24 h). Basal plasma ACTH levels (mean, 162 pg/ml; range, 12.1–3300 pg/ml; mean, 36 pmol/liter, range, 2.7–724 pmol/liter) were normal in 32% of patients and increased in the remainder (54 of 79). Mean serum potassium was 3.8 mEq/liter (range, 2.0–5.4 mEq/liter). Seventy-four percent of patients were either hypokalemic at presentation or had evidence of prior hypokalemia based on potassium therapy.

Differences were noted in biochemical findings among

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TABLE 2. Baseline laboratory results from the initial visit of patients with CS caused by known or presumed ectopic ACTH secretion (unknown/occult)

	Units	Normal range	Patients with known source of ectopic ACTH secretion (69 of 73 patients)				Patients with unknown/occult source of ectopic ACTH secretion (16 of 17 patients)	
			Diagnosed within 6 months (n = 46)		Diagnosed after 6 months (n = 23)			
			Mean	Range	Mean	Range	Mean	Range
Serum K^+	mEq/liter	3.3–5.1	3.8	2.0–5.2	3.7	2.5–4.8	4.0	2.9–5.4
	(mmol/liter)	(3.3–5.1)	(3.8)	(2.0–5.2)	(3.7)	(2.5–4.8)	(4.0)	(2.9–5.4)
Urine cortisol	μg/24 h	24–108	3,189	59–20,952	4,426	168–35,000	2,425	207–11,500
	(nmol/d)	(70–300)	(8,810)	(160–57,620)	(12,170)	(460–96,250)	(6,670)	(570–31,770)
Urine 17OH corticosteroids	mg/24 h	2.0–10.0	53.3	1.8–193	55.1	12.4–113.5	40.3	5.4–161
	(mol/24 h)	(6–28)	(147)	(5–532)	(152)	(34–313)	(111)	(15–444)
Plasma ACTH	pg/ml	9–52	205.5	12.7–3,300	108.8	12.1–444	116.3	13.1–723
	(pmol/liter)	(2–11)	(45)	(3–724)	(24)	(3–97)	(26)	(3–159)

Patients who had undergone bilateral adrenalectomy are excluded. Values are in conventional units; values in SI units are in *parentheses*.

patients with initially overt ectopic ACTH-secreting tumors (diagnosed within 6 months), patients with initially occult but later diagnosed ACTH-secreting tumors (diagnosed after 6 months), and patients with presumed ectopic ACTH-secreting tumors (occult/unknown), but these did not reach statistical significance (Wilcoxon's test) (Table 2).

In 63 patients dexamethasone testing suggested EAS as follows: on the HDDST 30 of 35 (86%) and 31 of 33 patients (94%) failed to suppress UFC and 17OHCS, respectively, and 43 of 48 patients (90%) did not suppress plasma cortisol after O/N DST. After CRH administration 68 of 75 (91%) and 78 of 85 (92%) patients had no response of ACTH and cortisol, respectively. Fifty-four of 68 (79%) patients showed no responses to either dexamethasone or CRH; one had a positive response to both tests. Among the patients with previous TSS, two of 10 responded to HDDST or O/N DST and one of 12 showed a cortisol response to CRH. Only one of 67 patients showed a petrosal-to-peripheral ACTH gradient on IPSS. He subsequently was found to have an ethesioneuroblastoma.

Of 17 patients with occult EAS, one of six, two of nine, and four of 14 responded to HDDST, O/N DST, and CRH, respectively. None had an IPSS gradient, although three had abnormal petrosal venography. The rates of responses to these tests were not significantly different among patients with initially overt ectopic ACTH-secreting tumors (diagnosed within 6 months), patients with initially occult but later diagnosed ACTH-secreting tumors (diagnosed after 6 months), and patients with unknown/occult EAS (χ^2 test with Yates' correction). Furthermore, the rates of responses were not different among patients with carcinoid or neuroendocrine tumors, compared with patients with other tumors or patients with unknown/occult tumors (χ^2 test with Yates' correction).

Nine of 30 patients with carcinoid or neuroendocrine tumors had elevated urine 5-HIAA. Serum calcitonin was elevated in patients with medullary thyroid cancer (four of four, including the two patients with multiple endocrine neoplasia 2); carcinoid tumors, small-cell lung cancer, and pheochromocytoma (18 of 22); neuroendocrine tumors (two of four); gastrinomas (one of two); and occult disease (three of eight).

Imaging

All imaging modalities gave occasional false-positive results. CT and MRI localized the ACTH-secreting tumor (n = 67 of 73 patients) or were consistently negative (n = 9 of 17) (Table 3). Twenty-one of 43 octreotide scans correctly identified a source of ACTH. Among patients with an occult tumor, three had positive octreotide scintigraphy (one of these had negative CT and MRI; of two with positive CT and/or MRI, one died and one did not return for follow-up); 10 had negative octreotide scintigraphy. Pituitary MRI revealed one olfactory esthesioneuroblastoma and was negative in 48 patients. Inconclusive findings in 17 patients included possible pituitary microadenoma or low signal/enhancement area.

Venous sampling

Eleven of 37 patients had a 2-fold or greater ACTH gradient in a selective vein, including pulmonary (n = 2), thymic (n = 5), neck (n = 1), hepatic (n = 1), and adrenal (n = 2) veins. All non-IPSS venous sampling corresponded to a readily imaged and subsequently identified ACTH source, except for a thymic vein step-up (19). In this patient, ACTH-secreting pulmonary tumorlets were found subsequently (33).

Medical treatment

Sixty-two patients received steroidogenesis inhibitors or a glucocorticoid receptor antagonist for 1 wk to 176 months to normalize clinical features and UFC excretion. Medications included ketoconazole, metyrapone, aminoglutethimide, opDDD (ortho, paradichlorodiphenyldichloroethane), etomidate, and/or RU 486 (25, 34) and were discontinued or changed because of side effects or inadequate inhibition. Metyrapone, RU 486, and ketoconazole were used alone in three, four, and 20 patients, respectively. Other patients received up to three medications simultaneously or sequentially. Steroidogenesis inhibition was the only treatment for 10 patients. Fifty-three patients underwent blockade before surgical treatment, 11 of them for more than 12 months. Parenteral etomidate controlled severe hypercortisolism in three patients (35).

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TABLE 3. Imaging studies in 90 patients with CS caused by ectopic ACTH secretion

ACTH-secreting tumor	n	Pituitary MRI	Chest		Abdominal		Scintigraphy		Correspondence of imaging with diagnosis
			CT[a]	MRI	CT	MRI	Octreotide	MIBG	
Thymic carcinoid	5	1/4	5/5	2/5	0/5	0/5	0/2	0/1	5/5
Pulmonary carcinoid	35	7/24	27/35	23/27	2/31	1/25	9/12	0/0	35/35
Appendiceal carcinoid	1	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1
Pancreatic carcinoid	1	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1[b]
Pulmonary tumorlets	1	0/1	1/1	1/1	0/1	0/1	0/0	0/0	1/1
Neuroendocrine tumor	13	3/9	4/12	4/10	5/13	4/11	6/10	0/0	9/13
Gastrinoma	6	0/5	1/3	0/1	6/6	3/3	2/2	1/1	6/6
Small-cell lung cancer	3	0/2	2/3	1/2	2/3	1/2	2/2	0/0	3/3
Olfactory esthesioneuroblastoma	1	1/1	1[c]/1	1[c]/1	0/1	0/1	1/1	0/0	1/1
Pheochromocytoma	5	2/4	0/4	0/2	5/5	2/3	0/0	1/3	5/5
Medullary thyroid cancer	2	1/1	2/2	2/2	2/2	2/2	1/1	0/0	2/2
Unknown/occult	17[d]	2/13	4/17	3/13	2/16	2/12	3/13	0/0	NA

NA, Not applicable; MIBG, ^{123}I-metaiodobencylguanidine.

[a] Performed at 5-mm thickness in all but two patients.

[b] Final diagnosis after positron emission tomograph scan done elsewhere.

[c] The patient had chest lesions (*Nocardia* pulmonary infection); CT and MRI imaging of the head showed a lesion in the anterior cranial fossa.

[d] Included as cases of unknown/occult EAS: one patient who was not operated because of progressing Alzheimer's disease and cognitive deterioration and one patient deceased due to *Pneumocystis carinii* pneumonia during diagnostic evaluation.

Surgical treatment

Within 6 months, the ACTH-secreting tumor was identified in 26 patients who had curative surgery, 13 patients who had noncurative surgery, and seven patients who had biopsy. In another four patients, surgery was noncurative and the tumor was not found.

After 6 months and up to 112 months later, the ACTH-secreting tumor was identified in 16 patients who had curative surgery, four patients who had noncurative surgery, and three patients who had biopsy. In another two patients, surgery was noncurative and the tumor was not found (Table 4).

To control hypercortisolism, 33 patients underwent bilateral or completion adrenalectomy.

Pathological findings

Patients with an identified source of ectopic ACTH secretion had a histopathological established diagnosis at the NIH, with the exception of four patients with thymic carcinoid, pulmonary carcinoid, gastrinoma, and pheochromocytoma who had a histopathological diagnosis before referral. Table 4 shows the pathological diagnosis and staging of tumors causing EAS. The size range (largest dimension) was: pulmonary carcinoids/tumorlets, 0.3–4.0 cm; thymic carcinoids, 1.0–5.0 cm; neuroendocrine tumors, 1.0–4.0 cm; pheochromocytomas, 3.0–7.0 cm; and gastrinomas, 1.5–5.0 cm. Fifteen pulmonary carcinoids were characterized as typical and 13 as atypical.

Results after initial evaluation

In most patients, the ACTH-secreting tumors (thymic and pulmonary carcinoids, neuroendocrine tumors, gastrinomas, pheochromocytomas, medullary thyroid carcinomas, and an olfactory esthesioneuroblastoma) were identified within 6 months. In some patients who initially were classified as having unknown/occult ACTH-secreting tumors (with negative imaging), subsequent imaging with CT or MRI finally pointed to the presence of these tumors (carcinoids, neuroendocrine tumors, or small-cell lung cancer) after repeated diagnostic work-ups from 6 months up to 12 yr later.

Adjunctive therapy

Six patients with pulmonary carcinoid and three with thymic carcinoid received external radiotherapy to the mediastinum. In four patients, radiotherapy was directed to the tumor bed, hepatic or osseous metastases, or an esthesioneuroblastoma. Radiofrequency ablation was used to treat hepatic metastases of one neuroendocrine tumor. Two patients received interferon, whereas six with metastatic pulmonary carcinoid, neuroendocrine tumor, small-cell lung cancer, or gastrinoma received chemotherapy with 5-fluorouracil, streptozotocin, cisplatin, etoposide, and/or adriamycin.

Cushing's syndrome and survival

The median duration of follow-up was 26 months (range, 0–226 months). The ACTH-secreting tumor remained unknown/occult in 17 patients. Three patients with typical pulmonary carcinoids, no lymph node involvement, and no radiotherapy relapsed 128 ± 13 (mean ± SD) months after surgery. Another with atypical pulmonary carcinoid, positive lymph nodes, and no radiotherapy relapsed after 48 months. One patient with neuroendocrine tumor of the carotid sheath and postoperative radiotherapy relapsed after 120 months. All five patients are alive.

Nineteen patients are known to be deceased: three of 35 with pulmonary carcinoid, two of five with thymic carcinoid, four of six with gastrinoma, two of 13 with neuroendocrine tumor, two of two with medullary thyroid cancer, one of five with pheochromocytoma, three of three with small cell lung cancer, and two of 17 with occult tumor. Patients with an unknown/occult source of EAS survived longer, compared with those with an identified tumor, particularly during the later phase of follow-up (Fig. 1). Among patients with an identified tumor, those with pulmonary ACTH-secreting tumors (excluding small cell lung cancer) survived longest (Fig. 1).

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TABLE 4. Surgical treatment of patients with ACTH-secreting tumors, duration of follow-up, and status

ACTH-secreting tumor	Disease stage: n	Sex (male/female)	≤6 months			>6 months			Bilateral adrenalectomy (surgery before referral)	Follow-up (months)
			Biopsy	Surgery		Biopsy	Surgery			
				Cure	No cure		Cure	No cure		
Thymic carcinoid										
Localized	1	0/1					1			57
Infiltrated lymph nodes	2	2/0		1	1					16
Metastatic	2	1/1			1				1	29–49
Pulmonary carcinoid										
Localized	17	7/10		9	1		6	1	4 (1)	1–212[a]
Infiltrated lymph nodes	17	11/6		11	3		2	1	3 (2)	1–133
Metastatic	1	1/0							1	17
Appendiceal carcinoid										
Localized	1	0/1					1		1	73
Pancreatic carcinoid										
Localized	1	0/1					1		1	78
Pulmonary tumorlets										
Localized	1	0/1					1		1	151
Neuroendocrine tumor										
Localized	5	3/2			1		4			10–74
Infiltrated lymph nodes	2	0/2		1	1				1	6–48
Metastatic	6	2/4	2		2			2	4	1–40
Gastrinoma										
Localized	1	1/0	1						1	35
Metastatic	5	2/3	2		2				3 (1)	8–226[b]
Small-cell lung cancer										
Metastatic	3	2/1				3			2	1–48
Olfactory esthesioneuroblastoma										
Localized	1	1/0	1							41
Pheochromocytoma										
Localized	4	1/3		4						5–39
Metastatic	1	0/1								16[c]
Medullary thyroid cancer										
Metastatic	2	2/0	1		1				2	1–15
Unknown/occult tumor										
Unknown localization	17	6/11			4			2	8 (1)	1–203[d]

[a] One patient died from acute myocardial infarction 1 wk after successful operation.
[b] One patient with MEN-2A (gastrinoma, medullary thyroid cancer, and pheochromocytomas) died with hepatic metastases of gastrinoma.
[c] One patient with MEN-2B (medullary thyroid cancer and pheochromocytoma) died with medullary thyroid cancer metastases.
[d] One patient died due to pulmonary embolism, and one due to multiple organ failure and *Pneumocystis carinii* pneumonia.

Discussion

Presentation and diagnosis

This series of 90 patients illustrates the broad clinical spectrum of ectopic ACTH secretion, which includes children and adults of both genders, and symptoms of weight gain and loss, menstrual irregularities, fractures, cognitive and psychiatric disorders, hypertension, infections, weakness, and bruising. As a result, patients often were evaluated by physicians of many specialties before the clinical diagnosis was entertained. Once considered, in general, the biochemical diagnosis of Cushing's syndrome was clear, based on elevated UFC or 17OHCS excretion; more than half of the patients had UFC concentrations at least 10-fold normal. There were no appreciable differences in biochemical findings among patients with initially overt ectopic ACTH-secreting tumors (diagnosed within 6 months), patients with initially occult but later diagnosed ACTH-secreting tumors (diagnosed after 6 months) or patients with occult tumors causing EAS. These findings differ from those of Wajchenberg *et al.* (1), who reported that patients with initially occult tumors had less severe biochemical features of ectopic ACTH secretion than those who had initially overt tumors.

Our finding that 13 of 90 patients (14%) had previous TSS illustrates the difficulty in discriminating EAS from Cushing's disease. This finding is similar to the 12% rate reported by Jex *et al.* (7). This misdiagnosis may result from positive responses to dexamethasone or CRH or from an abnormal pituitary MRI, as seen in 14 of 68 (21%) and 17 of 66 (26%) of our patients, respectively. One third of the patients had a normal basal plasma ACTH level, contradicting previous reports that elevated values characterize EAS (36). In this series, IPSS was the single best test for the diagnosis of EAS, correctly identifying 66 of 67 patients. Abnormal pituitary venous drainage, which may cause false-negative IPSS results, was excluded in most.

Six to 14% of our patients responded to dexamethasone and 8–9% responded to CRH testing, depending on the outcome measure. Because of the different threshold criteria used, these findings are at slight variance with previous studies, in which 59 of 190 patients (31%) responded to dexamethasone (1, 3–8, 15, 37–40), and four of 53 (7.5%) responded to CRH (3, 4, 41–43). As previously noted, most patients who responded to dexamethasone had pulmonary carcinoids. Our results of IPSS are similar to those of other studies (4, 9, 44, 45) and corroborate the view that IPSS, despite its shortcomings (its use is limited by the expertise

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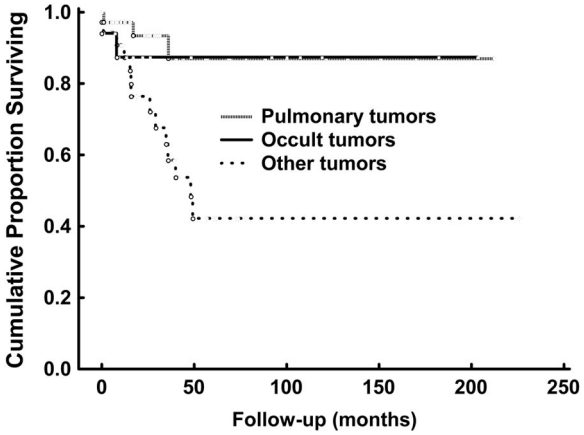

FIG. 1. Survival curves for patients with CS due to EAS for pulmonary ACTH-secreting tumors (including pulmonary carcinoids, tumorlets, and neuroendocrine tumors but excluding small-cell lung cancer; n = 38), occult source of EAS (n = 17), and all other causes of EAS combined (n = 35). Pulmonary ACTH-secreting tumors *vs.* other causes of EAS: $P = 0.003$; occult source of EAS *vs.* other causes of EAS: $P = 0.075$; occult source of EAS *vs.* pulmonary ACTH-secreting tumors: $P = 0.656$; Cox-Mantel test.

necessary to perform it, the high cost, and the rare neurologic and thromboembolic complications) has the highest sensitivity and specificity (approximately 94%; reviewed in Ref 46) for ruling out Cushing's disease.

Localization

Localization of an ACTH-secreting tumor is challenging. Despite extensive evaluation, a tumor was not identified in 17 of 90 (19%) of our patients. This percentage is slightly higher than the 12–16% rate reported by others (2, 44) and possibly reflects referral bias or limited follow-up. Alternatively some patients in this group of occult ectopic tumors might have Cushing's disease. The term occult has been used previously to refer to tumors that were not initially apparent but were found with continued observation (1). In this series, that group included foregut and appendiceal carcinoid tumors, neuroendocrine tumor, and small cell lung cancer, similar to the diagnoses reported in a 1994 review (1). Although these tumor types also presented as overt masses, all other tumor types were found at initial imaging. In this series ACTH was produced by an intrathoracic tumor in 47 of 90 (52%) of patients, similar to the rates of 41–60% in other series (1, 2, 8, 9, 44, 47). Apart from neuroethesioblastoma and appendiceal carcinoid, most other tumor types in this series (neuroendocrine tumor, gastrinoma, pheochromocytoma, medullary thyroid cancer, pancreatic islet cell and carcinoid tumors) have been reported by others at relatively similar rates (1, 2, 7). Tumors were best detected by CT or MRI (67 of 90; 74%). The standard 6 mCi octreotide scan had only 49% sensitivity (21 of 43) and did not detect any lesions not seen on CT or MRI. Our experience and that of others (1, 21) suggests that a single positive imaging study may represent a falsely positive result, whereas more than one positive study may confirm a true ACTH-secreting lesion. Thus, we recommend that CT, MRI, and octreotide scan all be used to screen for ACTH-secreting tumors. Non-IPSS venous sampling did not add to the information obtained with imaging studies; thus, we believe that venous sampling is not necessary for the evaluation of EAS except for IPSS.

Biochemical tumor markers were less helpful. Serum calcitonin, a marker for medullary thyroid cancer, was elevated in four of four patients with medullary thyroid cancer, 21 of 28 (75%) patients with identified and three of eight (38%) with occult ACTH-secreting tumors. Serum calcitonin was also found to be high in 44–69% of patients with EAS in previous reports (8, 9). Because calcitonin is known to be elevated in carcinoid and neuroendocrine tumors and to be within normal limits in patients with Cushing's disease (48, 49), it may be useful to discriminate EAS from other ACTH-dependent causes of Cushing's syndrome. Although increased excretion of 5-HIAA is classically associated with carcinoid tumors (50), only five of 19 patients with pulmonary carcinoids had elevated 5-HIAA urine levels. This discrepancy may be explained by the fact that foregut carcinoids lack L-DOPA-decarboxylase and thus do not produce 5-HIAA as frequently as midgut or hindgut carcinoids (51).

Management and prognosis

Hypercortisolism was associated with infection, present in 46 of 90 patients (51%) and the cause of two deaths, and pulmonary embolism, which caused death in one patient. Thus, these patients should be rigorously evaluated for infections, and prophylaxis for opportunistic infections and venous thrombosis should be considered.

The optimal treatment of EAS, surgical resection of the corticotropin-secreting tumor, was achieved in 59 of 90 patients (65%) within 112 months of diagnosis, and 42 were cured. Of the entire group, 29% had curative resection soon after diagnosis. This contrasts with the 12% curative resection rate reported in a large series from the Mayo Clinic (2). It is not clear whether this difference represents a difference in patient populations or a difference in the success of the localization strategy. Bilateral adrenalectomy to control hypercortisolism was required in 25 patients before and in eight patients after identification of tumor. In the former group, steroidogenesis inhibitors were ineffective, not well tolerated, or were rejected by the patients. In the latter group, residual tumor caused ongoing hypercortisolism.

The prognosis of EAS correlated with the tumor type. Extrathoracic neuroendocrine tumors, thymic carcinoids, small-cell lung cancers, medullary thyroid carcinomas, and gastrinomas usually were detected initially as overt tumors with metastatic disease. These patients died within 24.2 months on average. The ominous prognosis and short survival time for these tumors has been noted previously (4, 7). By contrast, pulmonary, appendiceal and pancreatic carcinoids and pulmonary or mediastinal neuroendocrine tumors tended to be initially occult and were less likely to metastasize, as previously noted (2). Patients with occult tumors had a good prognosis. Sixteen patients in this series (18%) died, 13 of them due to metastases.

Limitations

This study has limitations of accrual bias. It is likely that patients with overt tumor were referred less often than those with occult disease. Thus, estimates of the frequency of initial

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localization may be falsely decreased. Another limitation is the lack of consistent endocrine evaluation and imaging.

Conclusion

We conclude that the clinical spectrum of EAS is broad. Patients with EAS may be at risk from infections and venous thrombosis.

As shown here, IPSS or the combination of a negative 8-mg dexamethasone and CRH stimulation test both had high specificity to distinguish pituitary from ectopic ACTH secretion. To localize tumors that produce ACTH ectopically, CT and MRI of the neck, chest and abdomen are the primary imaging studies. Scintigraphy with [^{111}In]-pentetreotide can be a useful confirmatory modality.

The optimal treatment of EAS is surgical resection of the corticotropin-secreting tumor. Initial failure to identify a tumor is common, suggests pulmonary carcinoid or occult source of EAS, and has a favorable prognosis; prolonged treatment with steroidogenesis inhibitors may allow localization and cure. Small-cell lung cancer, medullary carcinoma of the thyroid, and gastrinoma are uncommon and present as overt masses with an ominous prognosis.

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