Cushing Syndrome Secondary to Ectopic Adrenocorticotropic Hormone Secretion

The University of Texas MD Anderson Cancer Center Experience

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BACKGROUND: Cushing syndrome (CS) secondary to ectopic adrenocorticotropic hormone (ACTH) secretion (EAS) has been described in association with a variety of tumors. The current experience with this syndrome was based on a few case series and individual case reports. Limited data were available about the tumors associated with CS-EAS in a cancer center setting. In this report, the authors have described their experience with CS-EAS at The University of Texas MD Anderson Cancer Center to further enhance the current understanding and management of this syndrome.

METHODS: This was a retrospective review of 43 patients with CS-EAS who were diagnosed between 1979 and 2009 at The University of Texas MD Anderson Cancer Center. RESULTS: Different neuroendocrine tumors were associated with CS-EAS. Twenty-one patients (48.9%) had tumors located in the chest cavity, with bronchial carcinoid and small cell lung cancer representing the 2 most common causes. The ACTH source remained occult in 4 patients (9.3%) despite extensive workup. Clinical presentation varied, and the classic features of CS were not evident in some patients. Death occurred in 27 patients (62.8%), and the median overall survival was 32.2 months. Major morbidities included new-onset or worsening hyperglycemia (77%), symptomatic venous thromboembolism (14%), and infections (23%).

CONCLUSIONS: In patients with CS-EAS who attended a comprehensive cancer center, tumors originating in the chest cavity were the leading tumors associated with this syndrome. The authors suspect that CS-EAS is under reported because of the atypical presentation in some patients. Thus, they suggest careful evaluation of patients with neuroendocrine tumors to avoid missing coexisting CS-EAS. Cancer 2011;117:4381–9. © 2011 American Cancer Society.

KEYWORDS: paraneoplastic syndrome, adrenocorticotropic hormone, Cushing syndrome, neuroendocrine tumors, localization studies.

Cushing syndrome (CS) in association with nonpituitary tumors was reported initially in 1928, shortly before Harvey Cushing reported his eponymous clinical syndrome associated with basophilic pituitary tumors in 1932. In the following 3 decades, multiple cases were reported in which adrenal hyperplasia was associated with various tumors, but the link between CS and ectopic adrenocorticotropic hormone (ACTH) secretion was not established until 1962.

Our current understanding of CS associated with ectopic ACTH production is derived mainly from the published series from large institutions as well as literature reviews and individual case reports. On the basis of the available literature, it is estimated that CS secondary to ectopic ACTH secretion (CS-EAS) constitutes 8% to 18% of all causes of CS. Many different of tumors, most neuroendocrine in origin, reportedly are associated with this syndrome. These tumors are readily apparent in many patients, although some require a great deal of time and effort to localize. There is some evidence that mortality is increased in patients who have CS-EAS compared with controls who do not have hypercortisolism. This excess mortality and morbidity may be caused in part by susceptibility to infection; however, prospective validation of these findings still is lacking.

The objective of the current review was to study our institutional experience with CS-EAS and to further our understanding of this clinical entity in a cancer center setting. To achieve this goal, we reviewed cases of CS to identify patients...
who had CS-EAS managed at our institution. We summarized their clinical features, diagnostic studies performed, long-term outcomes, and selected complications.

MATERIALS AND METHODS
A retrospective review of patients with CS was undertaken at the University of Texas MD Anderson Cancer Center after we obtained local institutional review board approval. Patients were identified through an institutional tumor registry database and from additional departmental databases. Initially, we searched for all patients with CS; then, we individually reviewed all patients to identify those who had CS-EAS diagnosed based on clinical documentation and diagnostic studies. Clinical data were obtained through a review of the medical records.

For the purpose of this review, CS-EAS was defined as: 1) ACTH-dependent CS (plasma ACTH >15 pg/mL) in patients who had tumors that had a known association with ectopic ACTH secretion; or 2) ACTH-dependent CS with positive ACTH immunostaining of nonpituitary tumors; or 3) ACTH-dependent CS with inferior petrosal sinus sampling (IPSS) that suggested an ectopic source, as determined by a central:peripheral ACTH ratio <2 at baseline or <3 after corticotropin-releasing hormone (CRH) stimulation.

We also reviewed records to summarize important clinical and laboratory parameters associated with CS, including hypertension, hyperglycemia, and hematologic and electrolyte abnormalities. New-onset or worsening hypertension was defined as an elevated systolic blood pressure at presentation (>140 mm Hg) in patients without a prior history of hypertension or clinical documentation of uncontrolled hypertension in patients with a pre-existing diagnosis of hypertension that had been well controlled on antihypertensive medications. New-onset or worsening hyperglycemia was defined as a fasting blood glucose level ≥126 mg/dL in patients without a prior history of diabetes mellitus or clinical documentation of worsening glycemic control in the 3 months before the diagnosis of CS. White blood cell counts and differentials at presentation were studied and classified as follows: Leukocytosis was defined as a white blood cell count >11,000/mm³, neutrophilia was defined as a neutrophil count >7300/mm³, lymphopenia was defined as a lymphocyte count <1000/mm³, and eosinopenia was defined as an eosinophil count <40/mm³.

Hypokalemia was defined as a serum potassium level <3.5 meq/L at presentation or the need for potassium supplementation or potassium-sparing agents to normalize potassium. Alkalosis was defined as a serum bicarbonate level >30 meq/L at presentation.

Statistical Analysis
The primary analysis was to determine the overall survival (OS) of patients with CS-EAS. For OS, the time to death or censoring was calculated in months after the date of CS-EAS diagnosis. In the absence of death, survival was censored at the date of last known follow-up. Univariate Cox proportional hazards regression was used to model the association between sex and duration of OS. The Kaplan-Meier product-limit method was used to estimate median OS. Statistical analyses were performed using STATA/SE version 11 statistical software (Stata Corp., College Station, Tex).

RESULTS
Patient Characteristics
In total, 300 patients with CS were identified, including 43 patients with ACTH-dependent ectopic CS who had been diagnosed between 1979 and 2009. Patients’ clinical features at presentation are summarized in Table 1.

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<th>Diagnostic Tests for CS</th>
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<td>Results from a 24-hour urine free cortisol (UFC) test were available, and UFC levels were elevated in 30 patients.</td>
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The median UFC level was 498 μg/24 hours (range, 71.7-12,515.0 μg/24 hours; upper reference value, 50 μg/24 hours). Random plasma ACTH levels were available in 42 patients. The median ACTH level at presentation was 182.5 pg/mL (range, 43-5900 pg/mL; upper reference value varied from 46 pg/mL to 52 pg/mL on different assays used during the review period). The ACTH value was not available at presentation in 1 patient who had a metastatic bronchial carcinoid tumor associated with a classic clinical presentation of CS and elevated cortisol.

Results from high-dose dexamethasone suppression tests (HDDSTs) were available for 16 patients, including 14 patients who had 8:00-AM serum cortisol values >5 μg/dL and 2 patients who had serum cortisol values <5 μg/dL after completing either 2-day or overnight HDDSTs. Cortisol levels in 8 patients after HDDST revealed a median 16.6% decrease (range, 2.8%-54.8% decrease) from baseline values.

The median change in peripheral plasma ACTH during an IPSS study (ACTH at 10 minutes after CRH injection compared with the baseline value) was 4.9% (range, 50%-81.5%). The change was <50% in 7 of 8 studies. In 1 patient, the increase was 81.5%, but the patient had a peak peripheral plasma ACTH level of 69 pg/mL and previously had no change in peripheral plasma ACTH after CRH injection during an earlier IPSS study.

### Tumor Distribution and ACTH Source

Tumors associated with EAS were distributed as follows: 9 patients (21%) had bronchial carcinoid tumors, 9 patients (21%) had small cell lung carcinoma (SCLC), 5 patients (11.6%) had medullary thyroid carcinoma (MTC), 3 patients (6.9%) had thymic carcinoid tumors, 6 patients (14%) had gastrointestinal neuroendocrine tumors (GEP-NETs), 4 patients (9.3%) had genitourinary tumors (2 prostatic NETs, 1 bladder NET, and 1 ovarian endometrioid carcinoma), 3 patients (6.9%) had widely metastatic NETs of unknown primary origin, and 4 patients (9.3%) had occult sources of ACTH despite extensive testing. Table 2 summarizes the tumors associated with CS-EAS in our series compared with other series in the English literature.

### Localization Studies

Several different localization studies were used, particularly in patients for whom the source of ACTH was not apparent at presentation.

### IPSS

Eight patients underwent IPSS, and the results provided further support for a diagnosis of EAS because of a lack of central-to-peripheral ACTH gradients in all 8 patients.

### Octreoscans

Twenty patients had 6-mCi indium-111 pentetreotide scans (octreoscans) obtained, including 8 patients who underwent this scan at least twice. Octreoscans identified the source of ACTH production in 12 patients (60% of those tested). This included 5 patients with bronchial carcinoid, 2 patients with medullary thyroid carcinoma, 3 patients with pancreatic NET, 1 patient with urinary bladder NET, and 1 patient with small bowel carcinoid. Octreoscans were negative in the remaining 8 patients (40%), including 4 patients who had an occult source of ACTH, whereas other imaging studies localized
an ACTH source in the remaining 4 patients (1 patient with bronchial carcinoid, 2 patients with thymic carcinoid, and 1 patient with a widely metastatic NET of unknown primary origin).

[18F]fluoro-2-deoxy-D-glucose–positron emission tomography

Six patients had [18F]fluoro-2-deoxy-D-glucose–positron emission tomography (FDG-PET) scans obtained. The underlying tumor was observed on FDG-PET scans in 4 patients (SCLC, thymic carcinoid, bronchial carcinoid, and MTC in 1 patient each), whereas the scan was negative in 2 patients (1 with a bronchial carcinoid tumor and 1 with an occult ACTH source).

Pituitary imaging

Thirty-four patients had pituitary imaging studies obtained, with normal results in 31 patients (91%) and incidental pituitary abnormalities identified in 3 patients (9%). IPSS failed to localize ACTH secretion to the pituitary in 2 of these 3 patients with occult ACTH sources. In the third patient, an incidental, 0.3-cm pituitary microadenoma was identified on a magnetic resonance imaging (MRI) study, and she was diagnosed subsequently with an ACTH-producing bronchial carcinoid tumor.

Cross-sectional body imaging

Chest imaging (computed tomography [CT] and/or MRI studies) localized the source of ACTH in 25 of 37 patients who had such imaging. These patients had their primary tumor located in the chest or lower neck and included 9 patients with bronchial carcinoid, 9 patients with SCLC, 4 patients with MTC, and 3 patients with thymic carcinoid. Abdominal imaging (CT and/or MRI) studies localized the source of ACTH or distant metastases to the abdomen in 9 of 32 patients who had such imaging studies.

Duration to ACTH Localization

The time to ACTH localization after CS diagnosis varied and ranged from 0 months to 118 months. The times to localization were as follows: Localization was observed at the time of diagnosis (within 1 month) in 32 patients (74.4%), and delayed localization (>1 month) was observed in 7 patients (16.3%) who had tumors that were localized after a median of 22 months (range, 6-110 months). The diagnoses of these patients were bronchial carcinoid tumors (4 patients), thymic carcinoid tumor (1 patient), bladder NET (1 patient), and 1 metastatic NET of unknown primary origin (1 patient).

Occult Source

In 4 patients (9.3%), the source of ACTH remained unknown despite extensive workup, and the patients were categorized with occult ACTH sources. Follow-up for these 4 patients ranged from 6 months to 118 months, and they had the following localization studies performed:

Pituitary imaging

Two patients had normal pituitary imaging studies, and 2 patients had images that suggested pituitary adenoma, but IPSS testing did not confirm adenomas as the source of ACTH. IPSS tests were done in all 4 patients, including 1 patient who underwent IPSS twice. Table 3 summarizes the biochemical profiles of these 4 patients.

Chest and abdominal imaging

Chest and abdominal cross-sectional imaging scans were negative in all 4 patients.

FDG-PET scans

An FDG-PET scan performed for 1 patient was negative.

Octreoscans

Octreoscans were negative in all 4 patients.

Management

Surgical and medical options to control hypercortisolemia were individualized considering the variability in ACTH sources. Twenty-eight patients underwent surgery, including 7 patients who underwent bilateral adrenalectomy, 14 patients who underwent resection of their primary tumors (ACTH sources), and 7 patients who underwent combined bilateral adrenalectomy along with primary tumor resection.

Medical therapy to control cortisol overproduction, which consisted mainly of metyrapone and ketoconazole, was offered to 40 patients with variable success. Available data did not allow a meaningful assessment of the response duration or magnitude considering the variability of the clinical course and the frequent deaths experienced in this cohort.

Medical Complications

Infectious complications were documented in 10 patients (23.3%), including 5 patients with pneumonia alone, 2 patients with pneumonia and cellulitis, 2 patients with pneumonia and sepsis, and 1 patient with septicemia. Symptomatic venous thromboembolism (VTE) was documented in 6 patients (14%), including 4 patients
with pulmonary embolism, 1 patient with unprovoked deep vein thrombosis of the axillary/subclavian veins, and 1 patient with symptomatic retinal vein thrombosis. Two patients with bronchial carcinoid died secondary to pulmonary embolism.

**Prognosis**

Death occurred in 27 patients, and the median OS duration was 32.2 months in all patients. There were no significant differences in median OS durations between men (32.2 months) and women (32.4 months; \( P = .714 \)). The Kaplan-Meier curve for OS in all patients is illustrated in Figure 1. Progression of primary malignancies and systemic infections at the time of death were the leading causes of mortality, and 2 patients died from pulmonary embolism.

**DISCUSSION**

Cushing syndrome in association with nonpituitary tumors was described more than 8 decades ago, but our current knowledge is limited to retrospective reviews in part because of the rarity of this syndrome, its variability in clinical presentation, and the heterogeneity of underlying tumors associated with this syndrome. Tumors associated with ectopic ACTH production have been well documented in the medical literature mainly in case reports and case series from single institutions. It remains uncertain whether patients who attend comprehensive cancer centers differ from patients reported from other tertiary referral centers. To clarify this uncertainty, we summarized our experience with patients with CS-EAS who attended and were treated at a comprehensive cancer center.

![Figure 1. This Kaplan-Meier curve illustrates overall survival for the entire series (n = 43). The median overall survival was 32.2 months.](image-url)
center and compared our findings with those from other case series at other major medical institutions. We identified a total of 300 patients with CS who attended and were treated in our institution, including 43 patients (14.3%) who had CS-EAS, a rate that is close to available reports in which CS-EAS constitutes 8% to 18% of all causes of CS. These estimates were derived mostly from major referral centers and probably are subject to referral bias.

The current body of literature reported the prevalence of clinical CS-EAS in 1.6% to 4.5% of patients with SCLC and biochemical abnormalities suggestive of CS or ectopic ACTH in as greater as 30% to 50% of patients with SCLC. Despite an extensive search of medical records, we identified only 9 patients who had SCLC-associated EAS-CS, and we could not reidentify previously reported cases of SCLC and CS published from our institution 2 decades ago. Therefore, we believe that our report underestimates the true prevalence of CS-EAS in patients with cancer.

Earlier reports have suggested that ectopic CS is more common in men, because initial cases of CS-EAS were often reported in patients with SCLC. However, our report and some other more recent case series have estimated that men constitute between 40% and 50% of all patients with CS-EAS and represent only 6% to 26% of patients with Cushing disease.

The median patient age at diagnosis was 48 years in our report. This falls within the range of mean ages at diagnosis (38-50 years) reported elsewhere. Clinically, weight gain was not universal in patients with CS-EAS, and weight loss was reported in 21% of patients in our series. This differs from the 10% of patients who reportedly lost weight in other series, and the discrepancy may be linked to the higher ratio of malignant tumors (especially SCLC) observed in our patients. The majority of patients in our series had new-onset or worsening hypertension or hyperglycemia, similar to what was observed in other reported series. Conversely, leukocytosis was identified in only 39% of patients in our series; whereas neutrophilia, lymphopenia, and eosinopenia were identified in 55% to 58% of patients at the time of initial diagnosis. Hypokalemia was noted in 72% patients in our study, which is similar to the reported prevalence of 71% in the literature. UFC and plasma ACTH levels were elevated in all tested patients, suggesting ACTH-mediated CS; whereas serum cortisol levels remained elevated in 88% of patients after HDDST, suggesting EAS and similar to the rates of 90% and 91% of patients reported by Ilias et al and Isidori et al, respectively.

The distribution of tumors associated with CS-EAS is summarized in Table 2. Looking at the combined data from multiple series in Table 2, it appears that bronchial carcinoid and SCLC tumors are the 2 most common causes of CS-EAS and represent approximately 44.4% of all cases. Thus, chest imaging represents the most important diagnostic test in patients who have ACTH-dependent CS with negative pituitary imaging or IPSS results suggestive of CS-EAS.

IPSS is a very helpful tool for ruling out pituitary sources of ACTH with very high sensitivity and specificity; however, the wider use of this procedure still is limited by the potential risk for serious complications and the availability of experienced neuroradiologists. After combining our data with 3 other reports, we observed that 37 of 38 patients with occult CS-EAS who had IPSS studies had no central/peripheral gradient suggestive of a nonpituitary source for ACTH secretion. However, this assumption should be viewed in the light of retrospective series in which false-negative IPSS results were observed in approximately 6.5% of patients with Cushing disease. Conversely, octreoscans localized the sources of ACTH in only 12 of 20 patients (60%) in our series, a rate that is close to other reports in the literature that indicated limited sensitivity for octreoscans in patients with CS-EAS. The use of FDG-PET is not established in the diagnosis and management of CS-EAS, although it is used often to stage and assess lung malignancies. Scattered reports have suggested the incidental finding of carcinoid tumors by using FDG-PET scans, with sensitivity of 75% to detect bronchial carcinoid tumors that measure 1 to 8 cm. The combination of FDG-PET with CT imaging reportedly enhanced the localization of bronchial carcinoid tumors. In the current series, FDG-PET localized ACTH sources in 4 of 6 patients (with SCLC, MTC, bronchial carcinoid, and thymic carcinoid tumors) in whom the primary tumor also was observed on less-expensive cross-sectional imaging studies. In the fifth patient, an FDG-PET scan was negative, as were all other imaging studies, at the time of diagnosis. With long-term follow-up, this patient had a 1-cm bronchial carcinoid tumor identified on a chest CT study 28 months after her initial diagnosis. In the sixth patient with an occult ACTH source, an FDG-PET scan was negative, similar to the other diagnostic studies. In 11 patients (25.6%), the diagnosis of the source of ACTH production was either delayed for >6 months or remained unknown after exhaustive workups. This finding is compatible with the overall experience reported in the literature, especially among patients with occult ACTH sources, as indicated...
in Table 2. Considering the complex nature of this disease, we suggested an algorithm for ACTH source localization (see Fig. 2).

Multiple questions remain unanswered regarding the association between infections and other medical complications previously reported in patients with CS. The association between CS and a predisposition to infection has been reported since the description of Cushing disease in 1932 by Harvey Cushing, who noted that patients with the syndrome were left with a definite susceptibility to infection. Ever since that report, retrospective evidence has accumulated to support the assumption of a higher risk of infection associated with hypercortisolism.15,16,33 We also observed an increased risk of infection in our series, but the lack of a good control group and the nature of retrospective data reviews may have affected the accurate assessment of the strength of this association between CS and infections.

The likelihood of VTE in association with CS has been debated; and, to date, the true prevalence has not been well established.34 It has been well documented that patients who have CS with altered coagulation-factor profiles, including elevated levels of coagulation factors II, V, VIII, IX, XI, and XII, are compatible with an increased risk of thrombosis.35 Despite the lack of quality evidence, a recent review suggested a risk of VTE in patients with CS of close to 2% in patients who did not undergo surgery and approximately 4% after surgery.36 It is unclear whether patients with CS-EAS have a higher risk of VTE compared with patients who have CS secondary to other causes. The finding that ectopic CS is associated with underlying malignancy theoretically may put these patients at greater risk for VTE compared with other CS patients. Still, our finding of 6 episodes of VTE (14%) is close to what was reported by others, who also combined prospective follow-up with retrospective analysis.34

The median OS in our series was 32.2 months, and we observed no effect of sex on survival. In our series, death occurred in 27 of 43 patients (62.8%) during follow-up, a death rate that was much higher than the reported rate of 21% (19 of 90 patients) in the National
Institutes of Health series, which included fewer patients with SCLC (3.3% of all patients). Nevertheless, our findings are similar to those published by Isidori et al, who reported that 25 of 40 patients (62.5%) died during follow-up; those authors noted deaths among 17.5% of patients with SCLC, which was close to our rate of 21%. Although CS with an occult ACTH source can lead to significant morbidity, OS is better in such patients than in patients who have apparent malignant sources of ACTH, including SCLC and MTC.

The heterogeneity of underlying tumors as well as the retrospective nature of our current study limited our ability to assess the effect of cortisol-lowering therapy on clinical outcomes, and especially on infections and death. We speculate that lowering cortisol levels before attempting curative treatments (surgery or chemotherapy) may reduce the mortality and morbidity associated with CS and, in particular, may reduce the rates of opportunistic infections. Prospective investigations of this syndrome are needed to fill the gaps in our knowledge related to CS-EAS and its effect on cancer-related therapy.

In conclusion, CS-EAS is a relatively uncommon clinical syndrome that accompanies a wide variety of tumors. Patients may not have obvious CS, because their clinical presentation may be masked by symptoms of the underlying tumor. Thus, the diagnosis can be challenging, and the source of ACTH production can be difficult to identify. In addition, the true prevalence of this syndrome probably has been underestimated in the current retrospective review. This syndrome is associated with significant morbidity and mortality, which may be related in part to the expected increased incidence of infectious and thrombotic complications. Patients with NETs need to be assessed carefully for CS-EAS. Prospective studies are needed to clarify the true prevalence of this syndrome in cancer patients and its clinical complications.

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CONFLICT OF INTEREST DISCLOSURES
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