

Meet the expert session

**Ectopic adrenocorticotrophic hormone dependent Cushing's syndrome: diagnosis and treatment**

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Endogenous Cushing's syndrome (CS) results from sustained pathologic hypercortisolism caused by excess adrenocorticotropic hormone (ACTH) from a pituitary adenoma (Cushing's disease; 70%), a non-pituitary ACTH-secreting tumor (ectopic ACTH secretion; 15%) or excessive cortisol secretion by an adrenal tumor (15%).

Diagnosis of CS is rarely made solely on clinical grounds, because no single symptomatology pattern is observed in all patients. Furthermore, clinical and laboratory features of CS overlap those of common entities and some patients have an atypical clinical presentation. Adding to the clinical dilemma are the serious consequences of unrecognized hypercortisolism. The chronic hypersecretion of cortisol causes central obesity, systemic arterial hypertension, impairment of glucose tolerance, dyslipidemia, and hypercoagulability and is associated with other co-morbidities, such as psychological and cognitive dysfunction, osteoporosis, and increased susceptibility to infection. The hypertension, hypercoagulability, and metabolic syndrome subsequently lead to increased cardiovascular risk, the main cause of heightened mortality in this patient population. Pathologic fractures are also common, occurring in 30–50% of CS patients.

Recently, several studies have suggested that prevalence of CS might be higher than previously thought. Increased awareness of the disease, leading to earlier diagnosis, coupled with targeted treatment should improve outcomes in the future.

After briefly discussing the patient screening process, this syllabus will focus on **localization of ACTH excess** and **treatment of ectopic ACTH dependent CS**. During the session we will review *illustrative clinical cases*.

## **DIAGNOSIS**

### **Initial testing**

Testing for CS is recommended in patients with multiple and progressive features compatible with CS and in patients with adrenal incidentalomas. The clinician remains the final arbiter in the clinical work-up for CS and it is the clinician who must put into context the history, physical and laboratory findings and arrive at the best possible diagnosis. If the physician is still undecided, a period of watchful waiting is always good advice with the thought that patients with true CS will continue to progress.

The following three approaches are used to **screen** for hypercortisolism: 1) assessment of cortisol secretion in a 24-hour period, 2) documentation of the loss of normal diurnal variation in cortisol secretion (late-night salivary cortisol), and 3) documentation of a loss of feedback inhibition of cortisol on the hypothalamic-pituitary-adrenal (HPA) axis (dexamethasone suppression testing). It is not unusual to require multiple tests to reach a conclusive diagnosis.

### **Confirmatory testing**

A **dexamethasone-corticotropin-releasing hormone (CRH) test** improves the accuracy of a low-dose dexamethasone suppression test. Initial experience with the test revealed that it was very effective in differentiating patients with pseudo-CS from those with CS. However, more recent studies have revealed a generally lower specificity than initial reports. Limitations and difficulties in interpreting data, including dexamethasone levels, should be taken into account.

### **Localization**

#### **ACTH independent vs dependent source**

Plasma ACTH levels distinguish ACTH-dependent from ACTH-independent causes of CS. A plasma **ACTH level lower than 5 pg/mL** with a serum cortisol level higher than 15 µg/dL indicates an **ACTH-independent source**. A plasma **ACTH level higher than 10 pg/mL** despite a serum cortisol level higher than 15 µg/dL suggests most likely an **ACTH-dependent cause**: pituitary hypersecretion of ACTH (Cushing's disease), ectopic ACTH-secreting tumors, or ectopic CRH-secreting tumors.

#### **CRH stimulation test**

CRH (1 µg/kg) is administered after ACTH and cortisol are measured at baseline and at 15 and 30 minutes and cortisol at 30 and 45 minutes thereafter. A 35% rise in ACTH and a 20% rise in cortisol together have a 90% sensitivity and specificity for a pituitary source of excess ACTH.

#### **8-mg dexamethasone suppression test**

High-dose dexamethasone overcomes feedback inhibition in pituitary tumors but does not in the majority of ectopic tumors. A greater than 68% suppression of serum cortisol has been reported to have 71% specificity and 100% sensitivity in identifying a pituitary source vs ectopic CS.

### **Inferior petrosal or cavernous sinus sampling (IPSS)**

Catheterization with central and peripheral measurements of serum ACTH levels simultaneously from both sides before and after CRH stimulation allows for a differential diagnosis between pituitary and ectopic ACTH sources. A ratio of  $< 2$  before and  $< 3$  after CRH is suggestive of ectopic source. This test is technically difficult and should be performed only at centers with a high level of experience. Several pitfalls in interpreting IPSS results will be discussed during the live session.

### **Tumor markers**

Measurement of **tumor markers**, including ACTH precursors may offer clinicians additional tools for the differential diagnosis of patients with ACTH-dependent CS, but further studies are needed.

### **Imaging**

It is essential to complete the imaging only after biochemical confirmation of hypercortisolism. Primary sites include the lung (bronchial carcinoids or small cell carcinomas), but can more rarely include the pancreas, thymus, gastrointestinal tract, and prostate as well as other tumors. See table below (“The various tumours which are associated with ectopic ACTH syndrome”; from Alexandraki, KI and Grossman, *AB Rev Endocr Metab Disord* (2010) 11:117–126).

<b>Tumor type</b>	<b>Percentage reported (%)</b>
Small cell lung carcinoma	3.3–50
Bronchial carcinoids	5–40
Islet cell tumors of the pancreas/ pancreatic carcinoids	7.5–25
Thymic carcinoids	5–42
Phaeochromocytoma	2.5–25
Medullary carcinoma of the thyroid	2–8

Tumor type	Percentage reported (%)
Other neuroendocrine tumors (gastrinoma, primary hepatic carcinoid tumours, spindle cell pancreatic endocrine tumors, olfactory esthesioneuroblastoma, paraganglioma, ectopic pituitary adenoma or disseminated with unknown primary)	≤5
Other miscellaneous tumors (squamous cell cancer of the lung, mesothelioma, small cell colon carcinomas, tumours of the esophagus, stomach, pancreas, larynx, trachea, salivary gland, prostate, leydig cell, breast, ovary, uterine cervix, kidney, gallbladder and anorectal cancer, hepatocellular carcinoma, melanoma, leukaemia, lymphoma, and osteomyeloma)	≤5
Tumor not identified	12–37.5

Finding the source of ectopic ACTH production can be challenging, as these tumors are typically small and radiographically covert on routine computed tomography (CT) imaging, but are apparent in some cases on high resolution CT scanning. Bronchial carcinoid tumors are usually ≤ 1 cm; therefore overlapping cuts of 1 cm or less should be used. ACTH-secreting thymic carcinoid tumors are generally > 2 cm and readily visualized by CT. If chest imaging is considered to be normal, it is necessary to perform extensive CT scanning of the abdomen to reveal other ACTH-secreting tumors, in particular, pancreatic islet cell tumors, intestinal carcinoid tumors, and pheochromocytomas.

Notably, pituitary incidentalomas and ectopic ACTH-secreting tumors can frequently coexist.

An **indium-111 octreotide scan** can help confirm a suspicious lesion. Although thoracic and abdominal thin section CTs are the best method to localize an occult ACTH-secreting neoplasm, somatostatin receptor ligand scintigraphy may identify a few tumors not visualized by CT or magnetic resonance (MR) imaging. Scintigraphy sensitivity varies in the literature as between 30-80%. Repeat scans are necessary during long-term follow-up in persistent occult disease. Another potential advantage of the octreotide scan is the fact that it allows for visualization of primary or metastatic lesions in abdomen, chest, neck or skull.

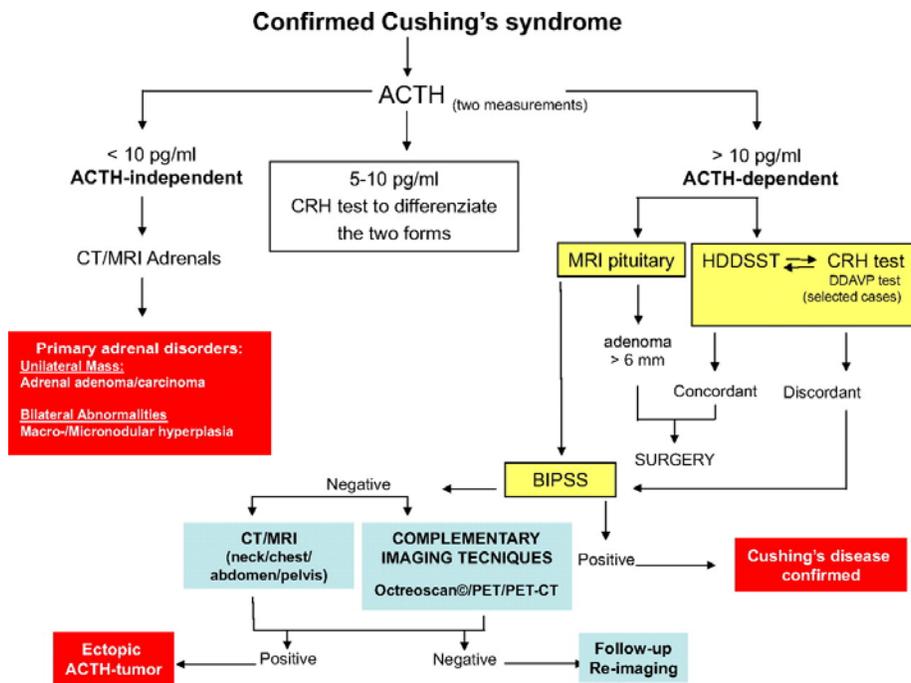
## Florine-18-fluorodeoxyglucose PET ([18-F]-FDG-PET).

The additional benefit conferred by [18-F]-FDG-PET for detection of ectopic ACTH-secreting tumors beyond conventional imaging modalities is controversial.

The use of  $^{11}\text{C}$ -5-hydroxytryptophan PET, Ga-68 DOTATATE, Ga-68 DOTANOC has been suggested in small studies; however further experience is needed.

Despite extensive investigation, the source of the ACTH hypersecretion may remain 'occult' in 5–15% of patients, and this requires continued follow-up. Over time, the number of patients remaining undiagnosed falls as tests are repeated, although identification of a tumor occasionally may take up to 20 years of follow up.

A clinical decision-making flow chart of differential diagnosis between ectopic CS and CD is illustrated below (Boscaro, M and Arnaldi, G *J Clin Endocrinol Metab* (2009), 94(9):3121–3131).



## TREATMENT

**Definitive treatment** involves **surgical resection of the primary ACTH secreting lesion**. In the case of ACTH-producing carcinoid tumors, this will induce both remission of symptoms and return of normal adrenal function. In a recent study, the probability of recovering

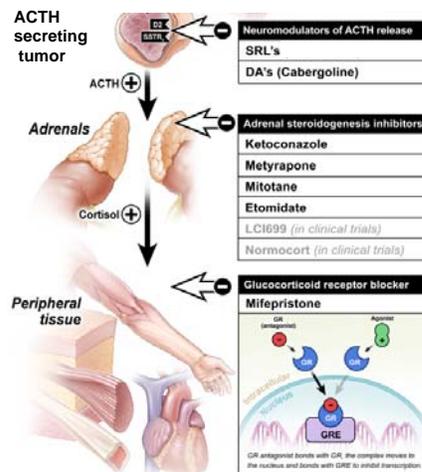
adrenal function in ectopic CS within 5 years of follow-up was 82%, much higher than either pituitary or adrenal CS.

Surgery is recommended even in the presence of metastatic disease, including localized liver metastases, if potentially resectable. When the primary lesion cannot be localized, treatment rests with medical or surgical attempts to control the symptoms of both carcinoid and CS.

**Bilateral adrenalectomy (BLA)**, preferably by an endoscopic approach is very effective in the rapid control of severe hypercortisolemia, especially in patients in whom the resection of primary tumor is not possible. It has been reported to be a safe technique for treatment of ectopic CS, nonetheless, the complication rate and postoperative mortality is higher in ectopic CS patients than in patients treated for benign adrenal disease or CD.

### Medical therapy

Hypercortisolism can sometimes be treated temporarily with adrenal steroidogenesis inhibitors or glucocorticoid receptor blocker (mifepristone). Below is a short summary of the therapeutic options; **further details regarding specific use of medical therapy, dose adjustments and adverse events will be discussed during the session.**



### Medical Therapy

**+Combinations**

Adapted from Fleseriu. *Neurosurg Clinics*. 2012

**Adrenal steroidogenesis inhibitors** Though not FDA approved, they have represented the mainstay of medical therapy in patients with ectopic CS. *Ketoconazole* and *metyrapone* are the most frequently used, but chronic treatment with these drugs can be limited by side effects like hepatotoxicity (ketoconazole) and increased androgen and mineralocorticoid production (metyrapone). *Etomidate* is the only available intravenous preparation and can be used to rapidly reverse cortisol excess in patients with acute complications. Recently, double and even triple **combination** of some of these drugs, as an alternative to urgent adrenalectomy, has been used for either short- or long-term in some patients. Hypoadrenalism is an important side effect following treatment with all adrenal steroidogenesis inhibitors and occasionally, might be necessary to institute a “block and replace” regimen.

*Mifepristone* (Korlym) is a **glucocorticoid receptor antagonist** at higher concentrations, with more than three times the binding affinity for the glucocorticoid receptor than dexamethasone. It also has progesterone receptor antagonist activity. Korlym is FDA approved for treatment of hyperglycemia associated with CS. Its use in patients with ectopic CS has been described in case reports and in few patients in a recent prospective open- label study (SEISMIC).

The change in the octreoscan uptake from negative to positive after successful mifepristone therapy in two patients with ACTH-producing bronchial carcinoids can be suggestive of a possible direct down-regulatory effect of glucocorticoid levels on tumoral somatostatin receptor type 2 expression.

### **Somatostatin receptor ligands (SRLs)**

*Octreotide* and *lanreotide* are currently the mainstay of treatment for carcinoid symptoms and they can also inhibit ACTH-secretion in ectopic CS, but clinical utility is somewhat limited, as hypercortisolemia induces down-regulation of somatostatin receptor type 2. A long- term response has been reported in few cases, as exemplified by a patient with recurrent lung carcinoid treated for 8 years. Interestingly, SRLs were shown to have a paradoxical effect on the ectopic secretion of ACTH in some cases. The role of a new SRL; *pasireotide* (approved for CD), in the treatment of ectopic CS remains to be defined, experience is currently limited to isolated case reports. Furthermore, a positive octreotide scan does not guarantee response to SRLs.

### **Dopamine agonists**

There are a few reports on the use of *cabergoline* (**dopamine agonist**) to treat ectopic CS.

### **Cytotoxic chemotherapy**

In patients with advanced, surgically non-resectable tumors, everolimus and sunitinib are **novel chemotherapeutic options** that might be of benefit in selected cases of ectopic CS.

### **Peptide receptor radionuclide therapy**

This has been also studied in a clinical trial as potential therapy for patients with somatostatin receptor expressing neuroendocrine tumors, but a role in ectopic CS has not yet been defined.

## **CONCLUSION**

The clinical presentation of CS varies widely. Although the diagnosis is straightforward in full-blown cases, establishing the diagnosis can be difficult in cases of mild hypercortisolism, especially as none of the signs or symptoms is pathognomonic of the syndrome. An elevated or inappropriately normal ACTH level reflects a pituitary or an ectopic source of ACTH as a cause of excessive cortisol. Differentiating between these two etiologies can be challenging.

If biochemical testing is discordant and a pituitary MRI is normal or equivocal (mass less than 6 mm), IPSS should be strongly considered. A search for an ectopic ACTH source is achieved by various imaging modalities. Localization and surgical excision of non-metastatic ectopic ACTH-secreting tumors leads to cure. Patients with occult ACTH-secreting tumors have a good prognosis, despite failure to localize their tumor, if adequate control of hypercortisolism is achieved. Hypercortisolism control is necessary in order to reduce morbidity and mortality. Adrenolytic medications may have a role in suppressing cortisol levels; however, success rate is lower than in other forms of CS. Recently, new therapies have been studied and more are in clinical development. However, bilateral adrenalectomy continues to be a very rapid and efficient way to control the disease.

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