Ectopic ACTH Syndrome: A Tertiary Care Center Experience

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Mexican Institute of Social Security, Mexico City, Mexico
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Disclosure

• Member of the Mexican Society for Nutrition and Endocrinology and the Endocrine Society

• Speaker for Sanofi, Ipsen and Novartis

• Currently not doing research for pharmaceutical companies
Epidemiology of Ectopic Cushing’s syndrome

Endogenous Hypercortisolism (Cushing’s Syndrome)

- 1 new case /million inhabitants /year
- Prevalence 40/mill
- Most are ACTH dependant and due to a pituitary corticotroph adenoma

~10% of all Cushing’s are ectopic

Of all ectopics
- 40% NET
- 20% SCLC

1/ 3-5 million

NET or tumors with endocrine Differentiation (PNS)

- 7-15% of all tumors have paraneoplastic syndromes (PNS)
- Few have endocrine PNS
- Cushing syndrome is uncommon

RARE DISEASE

Rare and complex diseases should be treated by multidisciplinary teams

Hypothalamus

¿CRH?

AVP

CRH

Pituitary

ACTH

Adrenal glands

Cortisol

Pathophysiology

Ectopic CRH

Ectopic ACTH
Pathophysiology

Abnormal Production

Secretion

Biological activity

Clinical syndrome

IHC

Tumoral marker

Hormonal assay

Patient, lab and imaging evaluation

Clines GA, et al. Hypercalcaemia. Hypercalcaemia of malignancy and basic research on mechanisms responsible for osteolytic and osteoblastic metastasis to bone Endocrine-Related Cancer (2005) 12 549–583
Oncologists consider Ectopic Cushing a paraneoplastic endocrine syndrome

A paraneoplastic endocrine syndrome is caused by hormone secretion in a tissue that
1. Should be autorregulated or produced at certain developmental stages
   (e.g. serotonin in a GEP-NET → eutopic)
1. Shouldn’t produce that particular hormone
   (e.g. ACTH in the lung → ectopic)
1. Is clinically relevant

– Hormones, cytokines and precursors are also deleterious
– Incidentalomas are also considered

PNS should fulfill the following criteria

- Evidence of an endocrine abnormality in a patient with a neoplasia
  + Symptoms are related to tumor burden
  + Hormones remain elevated when the gland is removed
  + There is a hormone gradient
  + Evidence of hormone in the removed tissue

Ectopic ACTH syndrome: perspectives

<table>
<thead>
<tr>
<th>Oncologists</th>
<th>Endocrinologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aggressive and poorly differentiated malignant tumors</td>
<td>• Well differentiated tumors</td>
</tr>
<tr>
<td>– Small or large cell carcinoma</td>
<td>– Neuroendocrine cells</td>
</tr>
<tr>
<td>– Frequently, terminally ill patient</td>
<td>– Evident Cushing’s syndrome</td>
</tr>
<tr>
<td>– CS may not be evident or the main concern</td>
<td>• First biochemical diagnosis</td>
</tr>
<tr>
<td>– First finding is the tumor</td>
<td>then imaging</td>
</tr>
<tr>
<td>• CS diagnosis requires a high index of suspicion</td>
<td>• Biochemical evidence guides</td>
</tr>
<tr>
<td>• Only biochemical evidence may be present but few signs or symptoms</td>
<td>follow up</td>
</tr>
</tbody>
</table>

Progression & dedifferentiation: merging views
Our Tertiary Care Center

• Mexican Institute of Social Security
  – 30% Mexican population

• Centro Medico SXXI
  – Only 2 tertiary care centers with advanced tools for endocrine diagnosis and Tx

• Endocrinology
  – 9 clinics
  – 1 basic investigation unit
  – ~ 100 patients/day
  – Neuroendocrinology
    Cushing & NET clinics

Hospital de Especialidades:
  0 oncologists
  1 endocrinologist

Oncology Hospital:
  1 endocrinologist
Hospital de Especialidades, Centro Médico Nacional S.XXI, Mexico City

- 1993-2016
  - 165 patients with Cushing’s syndrome
    - 144: Cushing’s disease (87%)
    - 14: EAS (8.5%)
    - 10: Identified NET
    - 4: Occult
    - 7: Adrenal adenomas (4.2%)

# Frequency of ectopic Cushing’s Syndrome in large ENDOCRINE series

<table>
<thead>
<tr>
<th>Author</th>
<th>n (Total)</th>
<th>Type of center</th>
<th>EAS n (%)</th>
<th>CD n(%)</th>
<th>Adrenal n(%)</th>
<th>Unknown source n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invitti Italy, 1999</td>
<td>426</td>
<td>Multicentric</td>
<td>25 (6)</td>
<td>288 (68)</td>
<td>113 (26)</td>
<td>-</td>
</tr>
<tr>
<td>Euro Cushing’s Registry, 2011</td>
<td>481</td>
<td>Multicentric</td>
<td>24 (5)</td>
<td>317 (66)</td>
<td>139 (27)</td>
<td>-</td>
</tr>
<tr>
<td>Yaneva Bulgaria, 2013</td>
<td>386</td>
<td>One center</td>
<td>12 (3.1)</td>
<td>240 (62.1)</td>
<td>124 (32.1)</td>
<td>10 (2.5)</td>
</tr>
<tr>
<td>Ammini India, 2014</td>
<td>364</td>
<td>One center</td>
<td>22 (6)</td>
<td>215 (59)</td>
<td>71 (19)</td>
<td>56 (15)</td>
</tr>
</tbody>
</table>

## Frequency of EAS
### Non Endocrine Series

<table>
<thead>
<tr>
<th></th>
<th>Year of Presentation (mean follow up)</th>
<th>Total Patients n</th>
<th>Patients with CS n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PULMONARY CARCINOID</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deb (Thoracic surgeons)</td>
<td>1966-1998 (32 y)</td>
<td>441</td>
<td>23 (5.2)</td>
</tr>
<tr>
<td>Amer (Thoracic surgeons)</td>
<td>1984-2004 (10 y)</td>
<td>90</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td><strong>THYMIC CARCINOID</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moran &amp; Suster (Pathologists)</td>
<td>1960-2005 (35 y)</td>
<td>80</td>
<td>5 (6.2)</td>
</tr>
<tr>
<td><strong>MEDULAR THYROID CA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbosa (Endocrinologists)</td>
<td>NA</td>
<td>1637</td>
<td>10 (0.6)</td>
</tr>
</tbody>
</table>

Clinical suspicion
Scrutiny: UFC + LDDT

Both negative
No Cushing’s syndrome

Both positive
Cushing’s syndrome

Discordant or suspected pseudocushing
Night cortisol

Localization: ACTH

<5 pg/mL
adrenal

>15 pg/mL
HDDT supression >68% + tumor

<1.8 mcg/dL
Night cortisol

>7.5 mcg/dL
Cushing’s syndrome

1.8 -7.5 mcg/dL
Pseudo Cushing

HDDT supression >68% + no tumor

CONTROVERSY
• Different protocols
• Cutoff points
• Correct positioning of catheters
• dDAVP vs CRH

ECTOPIC

HDDT supression >68% + tumor

Pituitary

ACTH >3:1

## High dose dexamethasone suppression test

<table>
<thead>
<tr>
<th>Publication</th>
<th>Test</th>
<th>Criteria of suppression</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dichek</strong> &lt;br&gt; JCEM 1994</td>
<td>8 mg DXM 23.00 h, Measure Cortisol 8 am</td>
<td>&gt; 50%  &lt;br&gt; &gt; 68%</td>
<td>88%</td>
<td>57%</td>
</tr>
<tr>
<td><strong>Flack</strong> &lt;br&gt; Ann Intern Med 1992</td>
<td>DXM x 6 days, Measure UFC</td>
<td>&gt; 50%  &lt;br&gt; &gt; 90%</td>
<td>90%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>HECMN S.XXI</strong> &lt;br&gt; 2008</td>
<td>8 mg DXM 23.00h Measure Cortisol 8 am</td>
<td>&gt; 50%  &lt;br&gt; &gt; 68%</td>
<td>81%  &lt;br&gt; 76-100%</td>
<td>71%</td>
</tr>
</tbody>
</table>

Usually ectopic tumors do not suppress higher than 80%.

There are no consensus or guidelines regarding the best test or cutoff.
Inferior Petreous Sinus Sampling
International experience

<table>
<thead>
<tr>
<th></th>
<th>Cushing’s Disease</th>
<th>Ectopic Cushing</th>
<th>False Negativ</th>
<th>False Positiv</th>
<th>Sensib %</th>
<th>Specif %</th>
<th>Technique OK %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980s</td>
<td>94%</td>
<td>6%</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1990s</td>
<td>75%</td>
<td>25%</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>2000s</td>
<td>78%</td>
<td>22%</td>
<td>0</td>
<td>0</td>
<td>85-100</td>
<td>66-100</td>
<td>99</td>
</tr>
<tr>
<td>2010s</td>
<td>96%</td>
<td>4%</td>
<td>0</td>
<td>0</td>
<td>66-100</td>
<td>50-100</td>
<td>93%</td>
</tr>
<tr>
<td>CMN-IMSS, 2017</td>
<td></td>
<td>20</td>
<td>7</td>
<td>4</td>
<td>94</td>
<td>100</td>
<td>97%</td>
</tr>
<tr>
<td>Unpublished data¹</td>
<td>(5 excluded)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alexandraki</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40%</td>
<td>77-84%</td>
<td>73-83%</td>
</tr>
</tbody>
</table>

## Characteristics of the patients with EAS vs CD (with pathology report)

<table>
<thead>
<tr>
<th>Variable</th>
<th>EAS and negative PSS</th>
<th>CD and positive PSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>35 (30-42)</td>
<td>34 (27-43)</td>
</tr>
<tr>
<td>UFC (mcg/24h)</td>
<td>879 (294-1635)</td>
<td>406 (289-624)</td>
</tr>
<tr>
<td>UFC index</td>
<td>8.75 (2.88-14.74)</td>
<td>2.96 (1.95-5.5)</td>
</tr>
<tr>
<td>% suppression with 8 mg DXM</td>
<td>17 (0-56)</td>
<td>57 (15-81)</td>
</tr>
<tr>
<td>Pre stimulation gradient</td>
<td>1.2 (1-1.38)</td>
<td>22.10 (7.31-26)</td>
</tr>
<tr>
<td>Post stimulation gradient</td>
<td>1.46 (1.27-2.03)</td>
<td>28.28 (16.44-50.70)</td>
</tr>
</tbody>
</table>


**UFC index**  
**Patient’s UFC**  
**UFC ULN**  

Suspect any result >ULN  
4x = diagnostic for Cushing’s syndrome
Localization of ectopic tumors

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary NET</td>
<td>37%</td>
<td>30%</td>
<td>32%</td>
<td>20%</td>
<td>25%</td>
<td>36%</td>
</tr>
<tr>
<td>Occult</td>
<td>20%</td>
<td>12%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>18%</td>
</tr>
<tr>
<td>Other NET</td>
<td>15%</td>
<td>10%</td>
<td>0%</td>
<td>0%</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>8%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Thymus NET</td>
<td>5%</td>
<td>5%</td>
<td>0%</td>
<td>40%</td>
<td>42%</td>
<td>0%</td>
</tr>
<tr>
<td>Pulmonary cancer</td>
<td>5%</td>
<td>18%</td>
<td>8%</td>
<td>0%</td>
<td>0%</td>
<td>18%</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>5%</td>
<td>4%</td>
<td>8%</td>
<td>10%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Medullary Thyroid carcinoma</td>
<td>2%</td>
<td>8%</td>
<td>16%</td>
<td>10%</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Appendix NET</td>
<td>1%</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Pancreatic NET</td>
<td>1%</td>
<td>8%</td>
<td>16%</td>
<td>20%</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Esthesioneuroblastoma</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Granuloma</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>18%</td>
</tr>
<tr>
<td>Other tumors</td>
<td>0%</td>
<td>0%</td>
<td>12%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
### Signs and symptoms associated with ectopic Cushing’s syndrome

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td>82%</td>
<td>56%</td>
<td>83%</td>
<td>Cushing symptoms 100%</td>
<td>54%</td>
</tr>
<tr>
<td>Weight gain</td>
<td>70%</td>
<td>42%</td>
<td></td>
<td></td>
<td>73%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78%</td>
<td>50%</td>
<td>100%</td>
<td></td>
<td>73%</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>78%</td>
<td></td>
<td></td>
<td></td>
<td>36%</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>75%</td>
<td></td>
<td></td>
<td></td>
<td>27%</td>
</tr>
<tr>
<td>Bone disease</td>
<td>75%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>71%</td>
<td></td>
<td></td>
<td></td>
<td>88%</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>53%</td>
<td>47%</td>
<td></td>
<td></td>
<td>63%</td>
</tr>
<tr>
<td>Echimosis</td>
<td>52%</td>
<td>42%</td>
<td>92%</td>
<td></td>
<td>9%</td>
</tr>
<tr>
<td>Infection</td>
<td>51%</td>
<td></td>
<td>17%</td>
<td></td>
<td>9%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>50%</td>
<td></td>
<td></td>
<td>50%</td>
<td>73%</td>
</tr>
<tr>
<td>Striae</td>
<td>44%</td>
<td></td>
<td></td>
<td></td>
<td>64%</td>
</tr>
<tr>
<td>Obesity</td>
<td>36%</td>
<td></td>
<td></td>
<td></td>
<td>73%</td>
</tr>
<tr>
<td>Edema</td>
<td>38%</td>
<td></td>
<td></td>
<td></td>
<td>9%</td>
</tr>
<tr>
<td>Fractures</td>
<td>30%</td>
<td></td>
<td></td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Acne</td>
<td>NA</td>
<td>28%</td>
<td></td>
<td></td>
<td>27%</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>19%</td>
<td>22%</td>
<td>25%</td>
<td>50%</td>
<td>27%</td>
</tr>
<tr>
<td>ACTH</td>
<td>157 pg/mL (12-3000)</td>
<td>166 (76-858)</td>
<td>221 (21-950)</td>
<td>high in 86%</td>
<td>108 (49-793)</td>
</tr>
<tr>
<td>Cortisol</td>
<td>3807 mcg/24h (59-35000)</td>
<td>45 (33-88)</td>
<td>NA</td>
<td>NA</td>
<td>29.7 (13.9-455)</td>
</tr>
<tr>
<td>K</td>
<td>3.8 mEq/L (2-5.2)</td>
<td>2.7 (2.1-3.4)</td>
<td>NA</td>
<td>NA</td>
<td>3.7 (2.6-4.4)</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>90</td>
<td>12</td>
<td>8</td>
<td>8</td>
<td>12</td>
</tr>
</tbody>
</table>
Ectopic tumors may have different time courses

*Includes a literature review*

Aniszewski. World J Surg 2001;25:934
Case 2 (P): 48 yo, female

2000
- Another hospital TSS

2001
- Thoracotomy
- Left adrenalectomy

2010
- Declined surgery

2012
- Lost follow-up

Histology:
- Negative for neoplastic tissue.
- Chronic inflammation

OCCULT NEUROENDOCRINE TUMOR
Made evident after adrenalectomy (Nelson-like effect??) or Normal tumor progression with time

Clinical CS

UFC 1,405 μg/d
Ovn LDDST 20 μg/dl
ACTH 99 pg/ml
Ovn HDDST 30%
ACTH ratio (IPSS) 1:1.7

( + ) CT left middle lobe
0.5 cm nodule
( - ) Octreoscan

( + ) CT left 1.4 X 1.8 cm nodule
( + ) Octreoscan left lung uptake

45 μg/d
1.2 μg/dl
54 pg/ml

70 μg/d
0.9 μg/dl
34 pg/ml

( + ) CT left 1.4 X 2.2 cm nodule
## Imaging studies for neuroendocrine tumors

<table>
<thead>
<tr>
<th>Study Method</th>
<th>Sensitivity(%)</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To detect primary tumor</td>
<td>73-93%</td>
<td>66</td>
</tr>
<tr>
<td>Metastases</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Details of metastasis</td>
<td>90-95%</td>
<td>74</td>
</tr>
<tr>
<td><strong>Low dose OCT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor nature</td>
<td>57</td>
<td>79</td>
</tr>
<tr>
<td><strong>High dose OCT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>89</td>
</tr>
<tr>
<td><strong>Ultrasound</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor burden and small tumors, biopsy</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td><strong>FDG/PET</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor nature</td>
<td>64</td>
<td>53</td>
</tr>
<tr>
<td><strong>68 Ga-DOTA/PET</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>97</td>
<td>92</td>
</tr>
</tbody>
</table>

Semskova, et al. JCEM 2010;95:1207
Hofman. Discov Med, 2012; 14(74):71-81
Isidori. J Clin Endocrinol Metab. 2015 Sep; 100(9): 3231–3244.
Other tests that may help in EAS

- Calcitonin and gastrin are commonly elevated in NETs regardless of tumor type
  - Calcitonin: 75% overt and 38% of occult EAS
- CgA & 5HIAA usually negative
- Intestinal peptides may be present (VIP, glucagon, somatostatin)
- Beta chorionic gonadotropin, alpha fetoprotein, carcinoembrionic agent: differential diagnosis
- Calcitonin and urinary catecholamines exclude MTC and phaeochromocytoma

**Limitations:**
- Not all EAS are typical NETs
- Tests are not specific for Ectopic ACTH syndromes
- No dynamic tests available

**Combination of several markers supports the diagnosis of a neuroendocrine tumor: at least one is elevated in 72%**
Histopathology of neuroendocrine tumors is variable.
Immunohistochemistry may help corroborate cell type and origin

Shahani S. Diagn Pathol. 2010; 5: 56.
Case 3 (FMR): 49 yo, male

2001
- Thorax Surgery
- Histology: Negative for neoplastic tissue, areas of pulmonary infarction

2003
- Thorax Surgery
- Histology: 0.5X0.5 cm Granulomatous lesion ACTH (-)

2014
- Thorax Surgery
- Histology: 0.7X0.3 cm Typical lung carcinoid ACTH (+)

Resection of atypical ACTH(-) mass resulted in clinical and biochemical remission, Eventual emergence of a subclinical ACTH + lesion
Treatment

• Radical excision of the tumour
  – Remission 83%
  – Complete resection 30–47%

• Adrenalectomy
  – 30–56% patients require surgery

• Adjuvant treatment
  – Inhibitors of cortisol secretion
  – Etomidate
  – Ketoconazol
  – Somatostatin analogues

Longest survival: recurrences and complications
Case 1 (DLC): 34 yo, female

2008

Thorax Surgery

Histology:
3.7 cm Neuroendocrine lung Carcinoma with 4 lymph node methastasis
ACTH (3+)

Classical Clinical CS

Thorax Surgery

Histology:
0.7X0.8 cm Neuroendocrine lung carcinoma with 1 lymph node methastasis
ACTH (+)

Chemotherapy

(+) CT: Mediastinal lymph conglomerate
(+) Octreoscan

2015

(+) CT: left lung apical mass 27.5 X 29.4 cm

2016

No clinical CS

Recurrent, metastatic, clinically and biochemically silent NEUROENDOCRINE TUMOR
Concluding remarks

• Ectopic Cushing’s Syndrome is a rare and complex disease
  – High index of suspicion if it is not a «classical Cushing’s syndrome»
  – Specific diagnostic tools should evolve to increase accuracy
  – Treatment and prognosis depend on the final diagnosis
  – Multidisciplinary & specialized medical-surgical teams should be the standard of management
If you have never missed the diagnosis of ACTH dependent Cushing syndrome, and you have never been fooled attempting to establish its cause, you should refer your patients with suspected hypercortisolism to somebody who has.

James Findling