# *Different aspect of Cushing syndrome from Diagnosis to Treatment*

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# *Agenda*

- *Case presentation*
- *Investigation of Patients With Suspected CS*
- *Cushing syndrome versus pseudo-Cushing*
- *Classification of Cushing syndrome*
- *Pitfalls in localization of  ACTH-dependent CS*
- *Follow up after TSS*

## *Illustrative Case*

A 62-year-old man presented with rapid evolution of symptoms, including depression, fatigue, weight loss and extreme muscle atrophy, over the course of a few months. Chart review revealed episodes of hypokalemia, hyperglycemia, pneumonia, metabolic alkalosis.

- Serum cortisol : 72 μg/dL (6.2–19.4 μg/dL)
- UFC : 1,656 μg/24 hours (5–64 μg/24 hours)
- ACTH: 135 pg/ml
- LDDST: serum cortisol: 11.1 μg/dL, UFC:25 μg/24 hours
- HDDST: serum cortisol: 71.8 μg/dL, UFC:1650 μg/24 hours

Which of the following is the most likely diagnosis ?

A) Pituitary adenoma

B) Ectopic ACTH syndrome

C) Macronodular adrenal hyperplasia

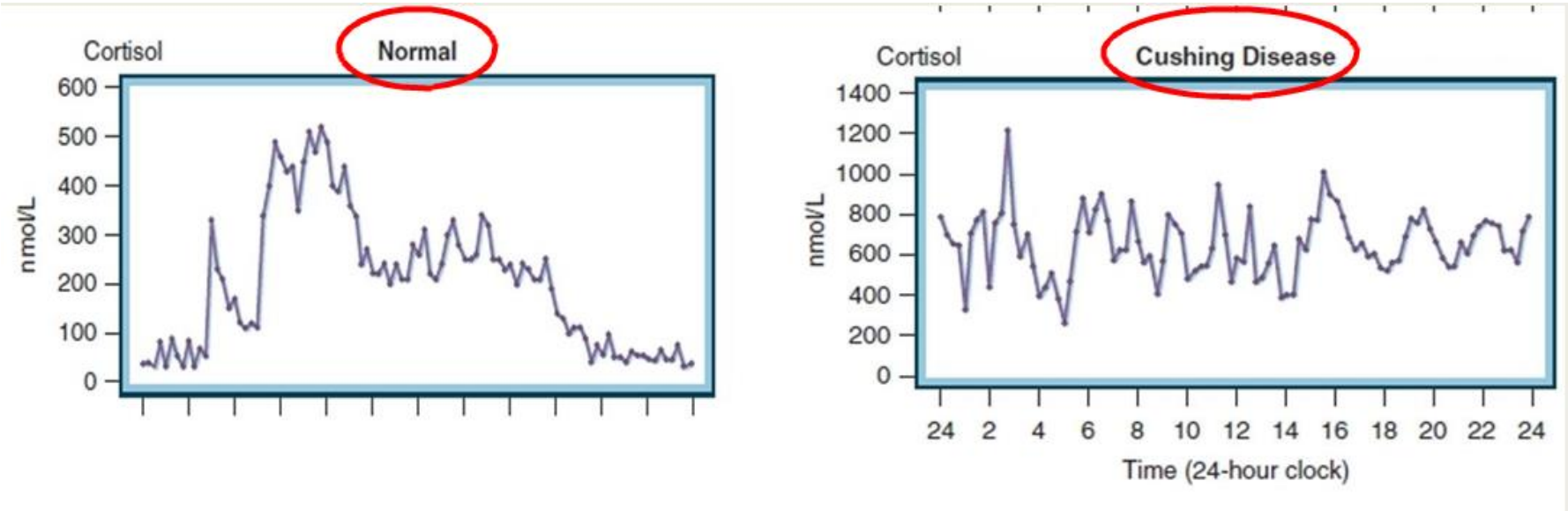
D) Adrenal carcinoma

# *Investigation of Patients With Suspected Cushing syndrome*

# *Screening tests*

- Overnight Dexamethasone Suppression Test
- Urinary Free Cortisol
- Circadian Rhythm of Plasma Cortisol
- Late night salivary Cortisol
- Low-dose Dexamethasone suppression Test

# *Circadian rhythm of plasma cortisol*




- Ideally patients should be hospitalized for 24-48 h before test
- A midnight cortisol >7.5 μg/dL indicates CS
- A midnight cortisol <2 μg/dL, excluded CS

# *Late night salivary Cortisol*

- Cortisole >2.0 ng/ml (5.0 nmol/L) have a 100% sensitivity and a 96% specificity for diagnosis of CS

- Avoid cigarette smoking, tobacco, steroid-containing lotion or oral gels on the day of collection

- Tends to increase with age & cardiovascular comorbid condition (HTN & DM), so the discriminating power diminishes in the elderly population

# *Cushing syndrome versus pseudo-Cushing*

## *pseudo-Cushing Syndrome1*

- Morbid obesity
- Poorly controlled DM
- Pregnancy
- Depression and other psychiatric conditions
- Alcohol dependence

# *Obesity*

- Simple obesity: Mildly increase in cortisol secretion rate, UFC is normal or mildly elevated

- CS screening in simple obesity is performed in the setting of poorly controlled HTN, DM, rapid progressive osteoporosis, hypokalemia

- 24-h UFC is a convenient screening test for CS in outpatient clinics

- ODST : is no longer recommended
  but suppression of plasma cortisol to <1.8 μg/dL excluded CS

# *Pregnancy*

- HTN and DM are the most common sign of CS in pregnancy
- Pregnancy is associated with a 3-fold increase in plasma cortisol,

  UFC also rises, and dexamethasone suppression test might be fail

- Recommend the use of late night salivary cortisol and UFC
- Against using dexamethasone suppression test

- Any adrenal or pituitary adenomas should be excised

- Metyrapone, not teratogenic, effective in controlling hypercortisolism

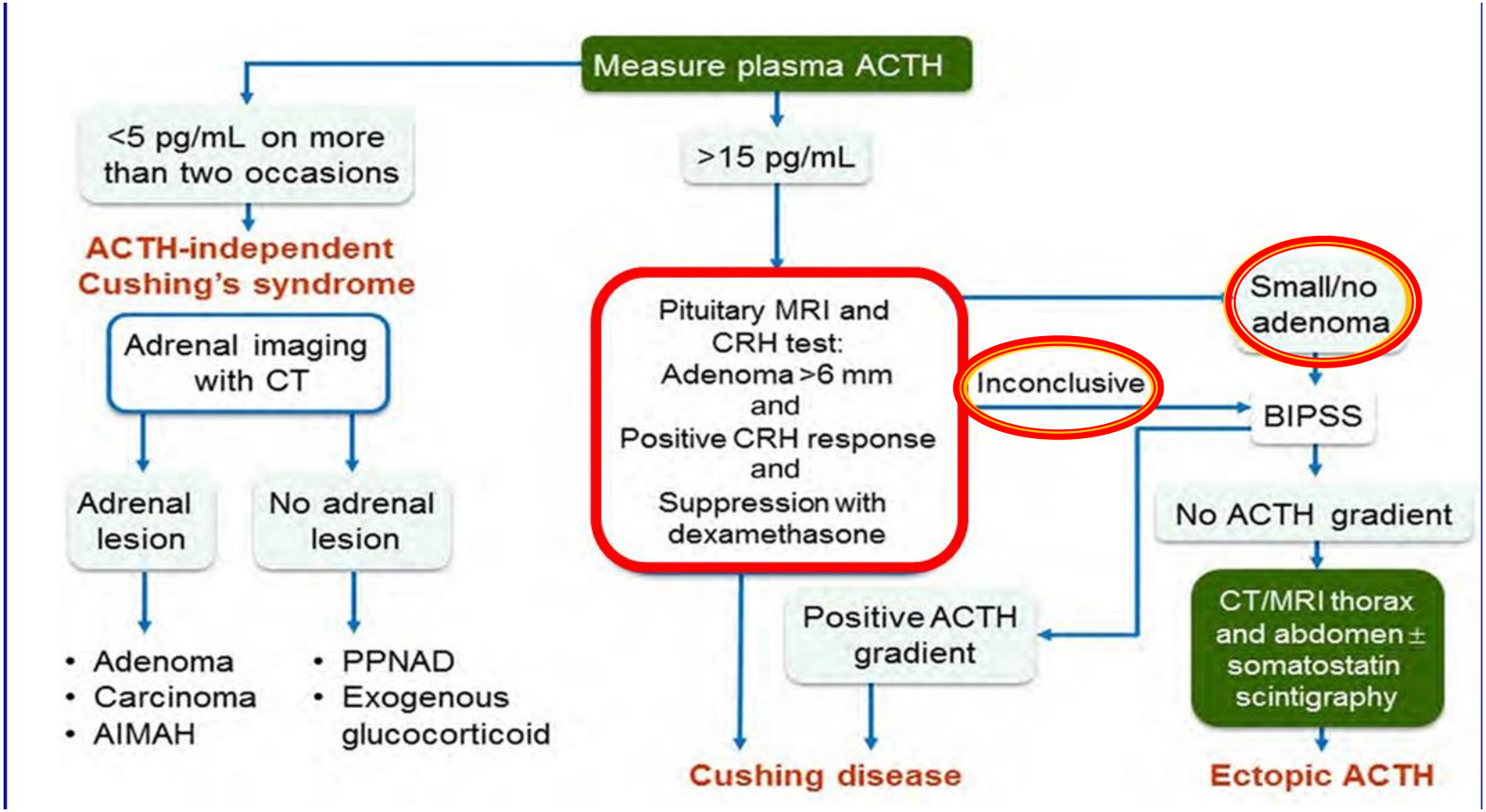
## *Pseudo-Cushing syndrome*

- Present with a similar clinical phenotype except
  - Cutaneous(easy bruising, thinning, friability)
  - Proximal muscle weakness
- The circadian rhythm of cortisol is preserved
- Treatment of underlying conditions leads to resolution of symptoms
- In clinical scenario, where the test results are discordant in a patient with mild hypercortisolism, F/U is recommended for monitoring progression of symptoms and for repeat testing

# *Classification of Cushing syndrome*

- ***ACTH –Dependent Causes***
  - Cushing disease
  - Ectopic ACTH syndrome
  - Ectopic CRH syndrome
  - Macronodular adrenal hyperplasia
  - Iatrogenic (treatment with 1-24 ACTH)

- ***ACTH –Independent Causes***
  - Adrenal adenoma and carcinoma
  - PPNAD and Carney syndrome
  - McCune-Albright syndrome
  - Iatrogenic (prednisolone, dexamethasone)


Measure plasma ACTH
<5 pg/mL on more than two occasions
ACTH-independent Cushing's syndrome
Adrenal imaging with CT
Adrenal lesion
No adrenal lesion
• Adenoma
• Carcinoma
• AIMAH
• PPNAD
• Exogenous glucocorticoid
>15 pg/mL
Pituitary MRI and CRH test:
Adenoma >6 mm
and
Positive CRH response
and
Suppression with dexamethasone
Small/no adenoma
Inconclusive
BIPSS
No ACTH gradient
CT/MRI thorax and abdomen ± somatostatin scintigraphy
Positive ACTH gradient
Cushing disease
Ectopic ACTH

# *Pitfalls in differential diagnosis of ACTH-dependent CS*

## *Pitfalls in differential diagnosis of ACTH-dependent CS*

- Severe CD Mimicking Classic Ectopic ACTH Syndrome
- Mild Ectopic ACTH Syndrome Mimicking Classic CD

# *Ectopic ACTH Syndrome*

- Rapid progression
- Weight loss
- More hyperpigmentation
- more substantial hypokalemia
- Greater degree of ACTH
- Greater degree of cortisol hypersecretion and UFC
- weaker cortisol suppression after  HDDST

## *Noninvasive biochemical testing*

### *1)HDDST*

- Up to 50% of patients with CD may fail to response to HDDST
- About 10% of patients with EAS show suppression of cortisol

50% (usually bronchial carcinoids)

### *2)CRH stimulation test*

- A response to CRH differentiate CD from other causes of CS
- Up to15% of patients with CD may be misdiagnosed by the test

## *3)Desmopressin stimulation test*

- Desmopressin, stimulates ACTH release in most patients with CD and usually induces a response similar to that of CRH
- up to 20 % of those with CD do not respond to this test

## *4)Combination testing with CRH /desmopressin and HDDST*

- If the two tests (CRH and/or desmopressin, and HDDST) both indicate CD, rare patients with ectopic ACTH secretion are falsely diagnosed, but a number with CD are missed

## *5) Pituitary MRI*

- A sensitivity of 80%
- Unable to find lesions in pituitary gland in 30-50% of CD patients
- Pituitary incidentaloma <6 mm are seen in 10-20% of the normal population

## *6)Bilateral inferior petrosal sinus sampling*

- Gold standard for DDX of pituitary or ectopic hypercortisolism
- Sensitivity of 88-100% , specificity of 67-100%
- Since ACTH secretion is intermittent, using CRH/Desmopressin increase the study's sensitivity

## *Indications of BIPSS*

- ACTH-dependent CS biochemically and NL pit MRI (no lesion, or a lesion < 6 mm)
- In cases without respond to hormone tests
- discrepancy between the biochemical and imaginal findings
- In post-hypophysectomy patients with persistent CS

# *Limitation of BIPSS*

- Invasive procedure
- Limited availability
- Rate of success depends on experience neuroradiological team

- False-positive:
  rarely in ectopic CRH syndrome
  adrenal tumor that pituitary ACTH is incompletely suppressed

- False-negatives :
  Poor catheter placement
  Anomalous or asymmetric venous drainage
  little initial experience
  tumors with cyclical ACTH secretion without respond to Desmo

# *Treatment of CD postoperatively follow up*

# *Surgical Treatment*

## *Cushing Disease*

- TSS: Remision rate in microadenoma is 70% -90%
  in macroadenoma is 50%
- Bilateral adrenalectomy (Nelson syndrome)

## *Ectopic ACTH Syndrome*

- Resection of tumor
- Bilateral adrenalectomy and monitoring

# *Radiotherapy*

- Is not recommended as a primary treatment except:

  - patients not responding to pituitary microsurgery
  - who have undergone bilateral adrenalectomy
  - patients with established Nelson disease

# *Follow up after TSS*

•perioperative and postoperative glucocorticoid covering is advised

•On days 2 to 5 postoperatively, a 9 AM plasma cortisol level should be measured with the patient having omitted glucocorticoid for 24-h

•Remission is generally defined as morning serum cortisol <5 μg/dL or UFC <10–20 μg/d postoperatively

• hypocortisolemic patients receive glucocorticoid replacement and education about adrenal insufficiency after surgical remission

# *Follow up after TSS*

•Re-evaluating other pituitary hormone deficiencies (serum Na ,free T4, prolactin)in the post operative period is recommended

• evaluate patients for possible CD recurrence when the HPA axis recovers, then annually, or sooner if clinical symptoms are present

• LNSC is more sensitive than UFC and DST for CD recurrence

•A postoperative pituitary MRI within 1–3 months after TSS is recommended

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## *Illustrative Case*

A 62-year-old man presented with rapid evolution of symptoms, including depression, fatigue, weight loss and extreme muscle atrophy, over the course of a few months. Chart review revealed episodes of hypokalemia, hyperglycemia, pneumonia, metabolic alkalosis.

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According to clinical presentation and laboratory results an ectopic cortisol source was suggested.

A chest and abdomen CT revealed two lung cysts, one of which was biopsied and was unremarkable for a lung tumor

Pituitary MRI showed 13 mm non-enhancing adenoma in right side

BIPSS demonstrated central gradient with right lateralization

After TSS, pathology revealed corticotropic pituitary adenoma staining strongly for ACTH and elevated Ki-67 proliferation index of 17%

Postoperative day 1 morning cortisol was 30.7 μg/dL, which progressively decreased to a cortisol level of 5.6 μg/dL at discharge on postoperative day 5. The patient was subsequently placed on steroid replacement

## *TAKE HOME MESSAGE*

- Differentiate CS from pseudo-Cushing with medical history, clinical examination, and biochemical test
- Radiological investigation should be avoided before proven CS
- Attention to pitfalls in localization of ACTH-dependent CS
- Close observation of patient with Cushing disease after TSS

*Thank you for your attention*