65 years old male with metastatic cancer

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HPI:

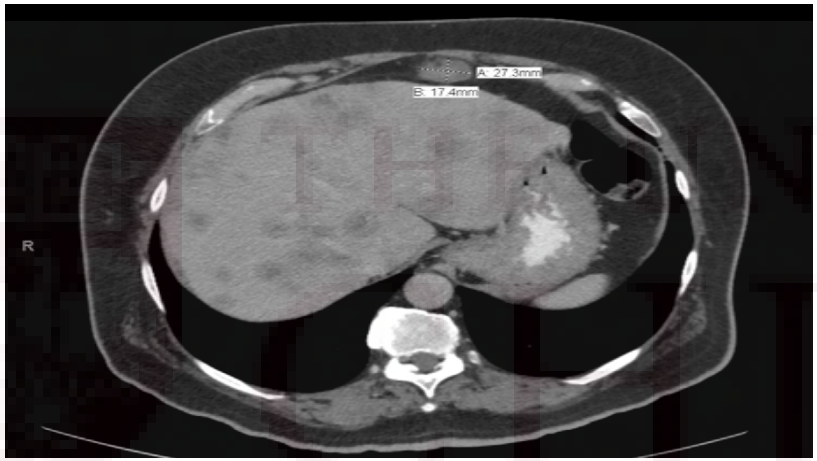
- The pt is a 65 y.o. Indian male who presented with weakness, fatigue, mood swings, insomnia, LE edema, urinary incontinence, poorly controlled BP and blood sugars for 1 month.

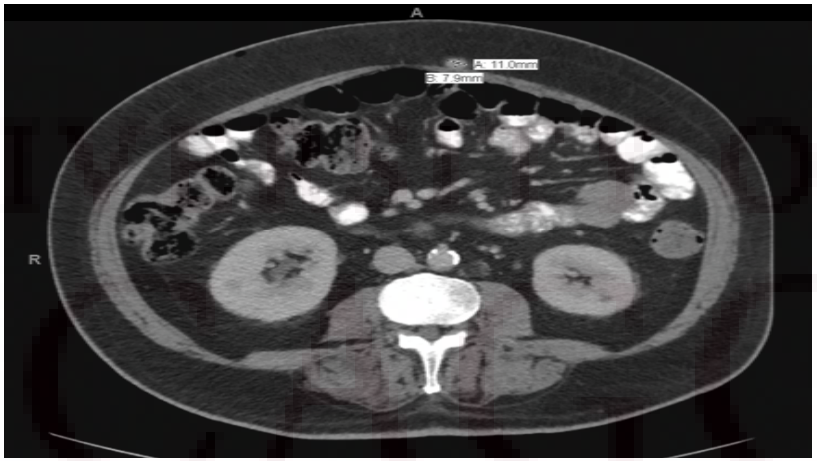
- In ER abdominal US was done and showed some nonspecific liver masses.

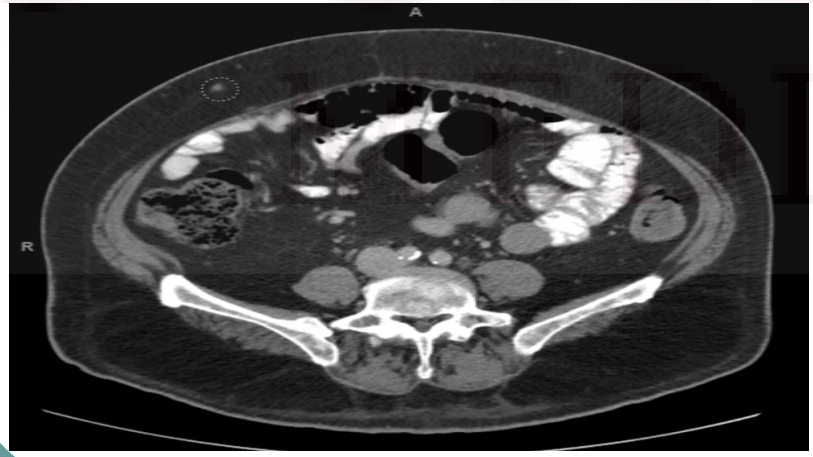
HPI:

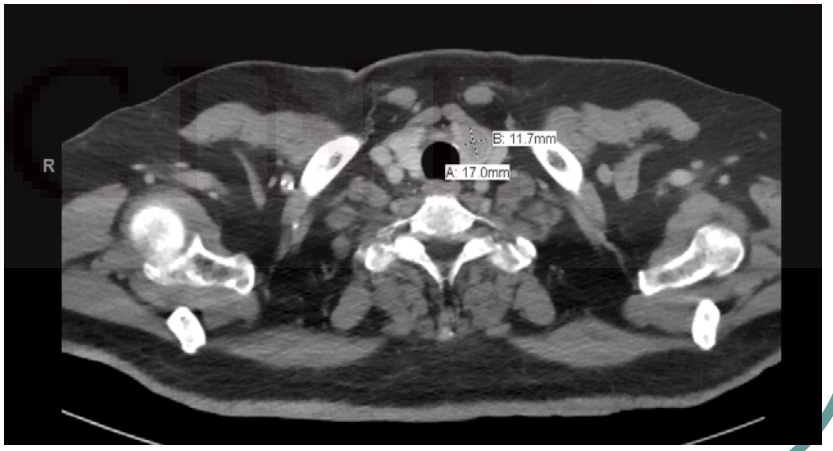
- CT chest/abdomen and pelvis was done and showed metastatic involvement of the liver, L adrenal thickening, few small L renal cysts, small nodular structure deep subcutaneous L paramidline abdominal wall, mildly enlarged L hilar lymph node questionable small faint focus in R upper pulmonary lobe.

CT abdomen and pelvis:

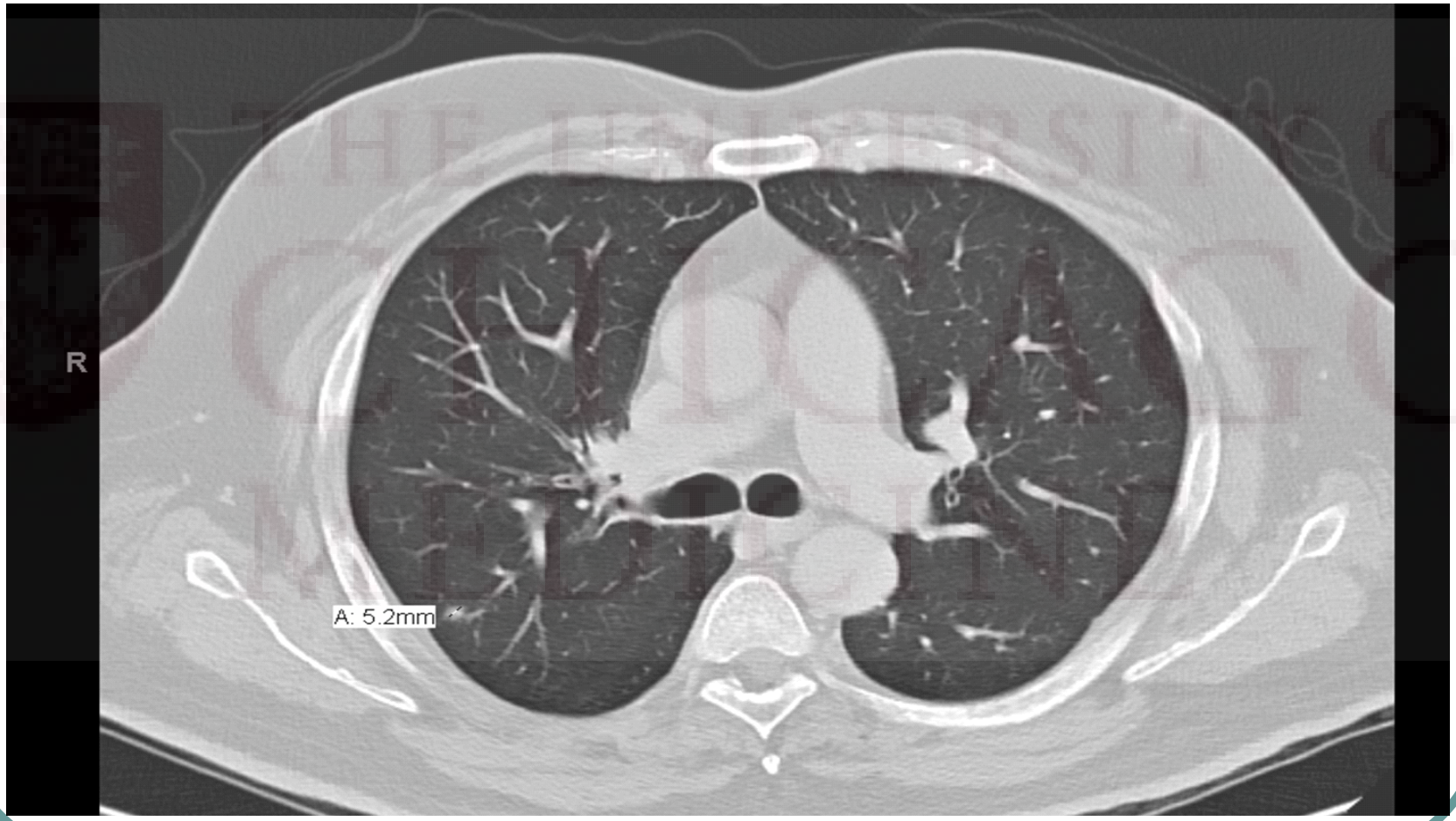








CT chest:



HPI:

- Colonoscopy was done and was negative for any masses
- IR guided liver biopsy was done

HPI:

- MRI brain showed 6mm focus in the L occipital lobe.
- PET scan showed:
  - mass lesions throughout the liver, increased metabolic activity in mediastinal, R hilar and retroperinoneal L nodes.
  - Osseous metastasis to midthoracic spine.
  - 2 subcutaneous nodules: subcutaneous soft tissue of the anterior abdominal wall to the L of midline, the second lesion was located posteriorly on the R near the level of thoracic inlet.

PMH:

- **PMH:**
  - DM2 for 20 years
  - HTN
  - Hypothyroidism
  - Hyperlipidemia
  - Vitamin D deficiency
- **SH:** physician, smoker (30 years 1PPD), no alcohol or drug abuse.
- **FH:** Maternal grandfather with DM2. Mother had a stroke at the age 85, CAD in his father at the age 43.

Medications:

- ASA
- Ergocalciferol
- Fluconazole
- Levothyroxine
- Lisinopril
- Metformin
- Lopressor
- Pantoprozole
- Rosuvastatin
- Insulin U-500 through insulin pump: BR 1 u/hr, CR 1:9, ISF 1:36, BS target 110.

Review of systems:

- Constitutional: **+Weakness and fatigue.** No recent weight changes.
- Eyes: No blurry vision.
- ENT: No thirst.
- Respiratory: No shortness of breath, cough.
- Cardiovascular: No chest pain, palpitations.
- Gastrointestinal: No nausea, vomiting, no abdominal pain, diarrhea.
- Genitourinay: **+Urinary incontinence.**
- Musculoskeletal: No myalgias. **+LE edema.**
- Skin: No rash, erythema. No stretch marks.
- Neurological: No headache. No peripheral neuropathy.
- Psych: +**mood swings, insomnia.**

Physical exam:

- Vitlas: BP 192/95, Pulse 99, Temp 36.6 °C , Resp 20, Ht 185 cm, Wt 117.482 kg, BMI 34.33 kg/m2, SpO2 98%
- Constitutional: No acute distress.
- Neck: Supple. No thyromegaly or nodules palpated.
- Cardiovascular: Regular rhythm and rate. No murmurs appreciated. Intact distal pulses.
- Respiratory/Chest: Normal respiratory effort. No wheezes or crackles.
- Gastrointestinal/Abdomen: Normoactive bowel sounds. Soft, nontender, nondistended. No hepatomegaly.
- Musculoskeletal/extremities: **LE edema 2+ bilaterally.**
- Neurological: Alert and oriented to person, place, and date. Normal deep tendon reflexes.
- Skin: Skin is warm and dry. **+Acanthosis nigricans noted on his face and neck.**

Labs:

142	103	18	79
3.5	26	0.8	

	12.6	
16.8		161
	39	

Ca 8.7 (8.4-10.2 mg/dL)
Mg 2.2 (1.6-2.5 mg/dL)
Phos 2.7 (2.5-4.4 mg/dL)

Total Protein 5.7 (6-8.3 g/dL)
Albumin 3.6 (3.5-6 g/dL)
Total Bilirubin 0.8 (0.1-1 mg/dL)
Bilirubin, conjugated 0.4 (0-0.3 mg/dL)
Bilirubin, unconjugated 0.1 (0.1-1 mg/dL)
Alk Phos 207 (30-120 U/L)
AST 99 (8-37 U/L)
ALT 189 (8-35 U/L)
HA1C 7.1%

TSH 1.94 (0.30-4 mcU/mL)

ACTH 223 (<52 pg/mL) at 12AM

Cortisol 62.1 mcg/dL at 12AM

24hrs urinary cortisol 941 (3.5-45 mcg/24hrs)

Labs:

CRH test:

	Minus 15 min	0 min	15 min	30 min	60 min	90 min	120 min	240 min
ACTH	121	117	117	124	123	127	122	126
Cortisol	26.8	27.5	27.4	29.5	29.5	31.2	30.2	31.9

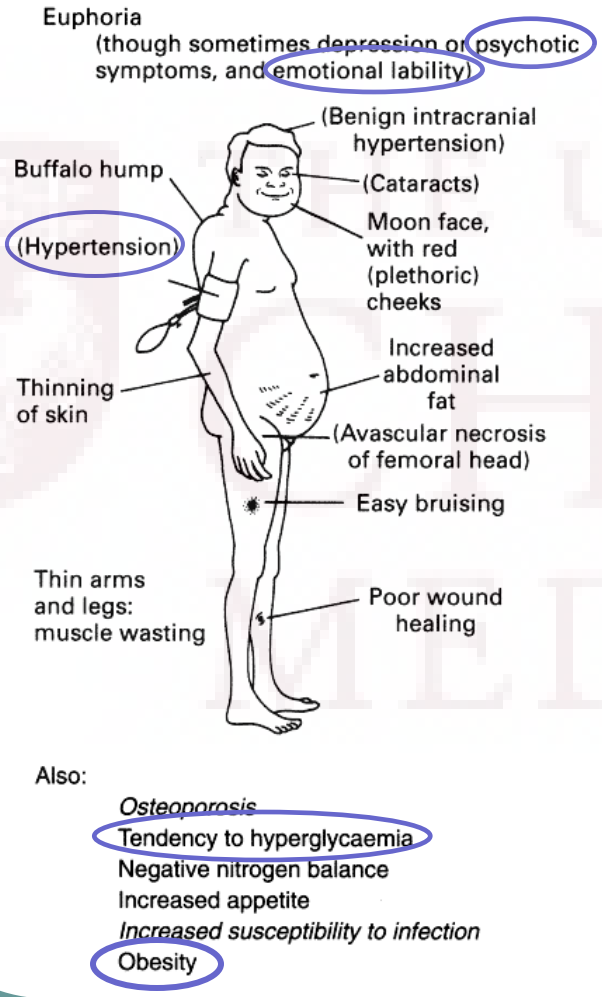
CRH test for diagnosis of ectopic ACTH:

- CRH test: ACTH increase >35% and cortisol >20% above baseline levels is considered to be a specific response for CD when ovine CRH is used,[1] and an increase >105% and >14% respectively when human CRH is used.[2]
- The CRH test has a sensitivity of 94% for cortisol and ACTH responses.
- 5%–17% of patients with EAS respond to CRH administration using a variety of cut-offs for cortisol and ACTH criteria.
- Most pts with CD respond to CRH within 45 min

[1] A simplified morning ovine corticotropin-releasing hormone stimulation test for the differential diagnosis of adrenocorticotropin-dependent Cushing's syndrome. Nieman LK, Oldfield EH, Wesley R, Chrousos GP, Loriaux DL, Cutler GB Jr. J Clin Endocrinol Metab. 1993 Nov;77(5):1308-12.

[2] Optimal response criteria for the human CRH test in the differential diagnosis of ACTH-dependent Cushing's syndrome. Newell-Price J, Morris DG, Drake WM, Korbonits M, Monson JP, Besser GM, Grossman AB. J Clin Endocrinol Metab. 2002 Apr;87(4):1640-5.

Summary:



- Elevated random ACTH and cortisol
- Elevated 24hrs urinary cortisol
- ,,Flat,, CRH test

- **Cushing's syndrome due to ectopic ACTH**

- Biopsy of the liver mass showed poorly differentiated small cell carcinoma.

- Immunohistochemical stain:

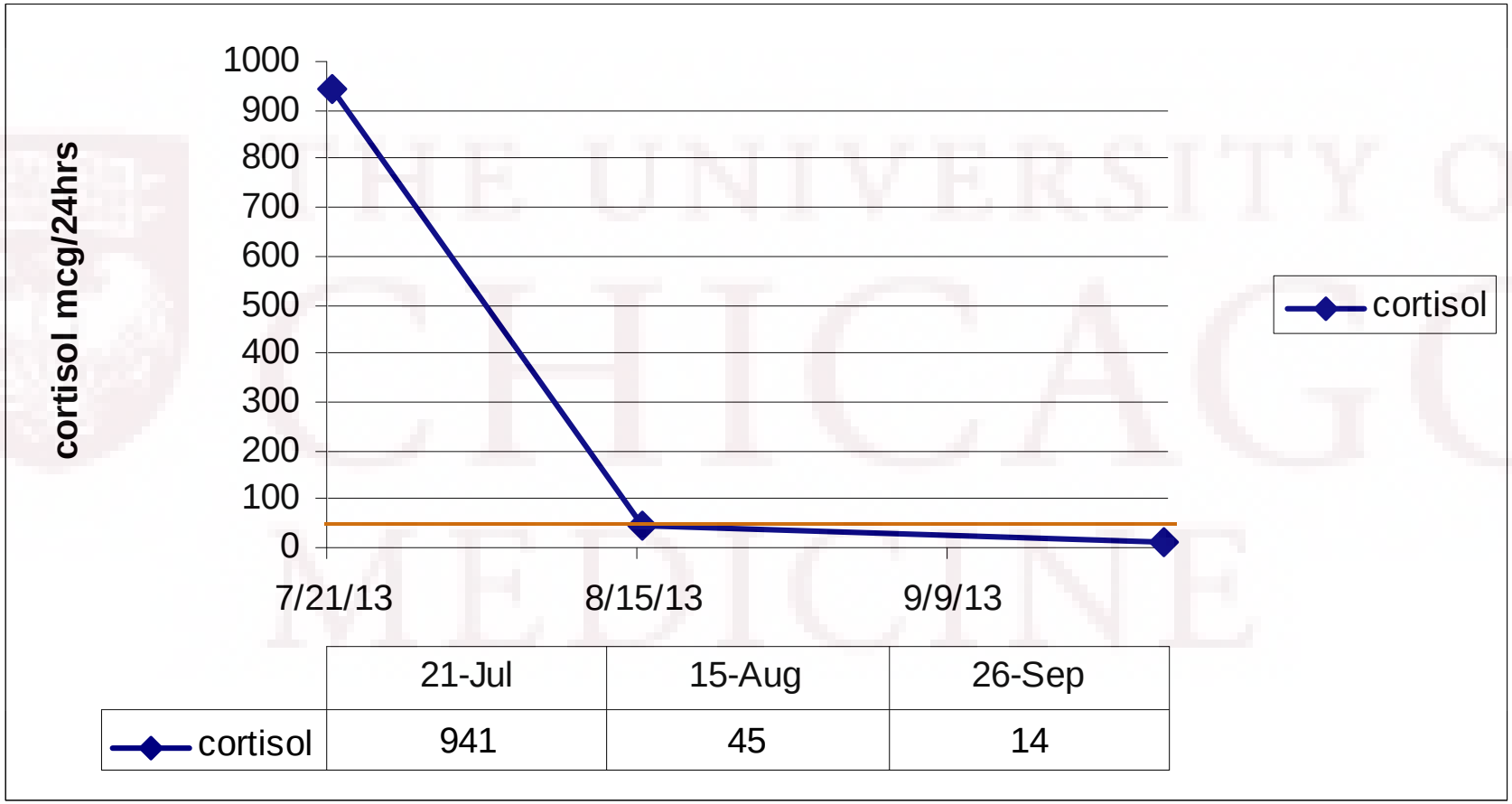
+ keratin, CD56, CK7, TTF1, weakly + chromogranin

- CD45, CK20 and synaptophysin.

How should ectopic ACTH be managed:

- Surgical excision of the tumor (could achieve 40% of cure rate)
- Medications (steroidogenes inhibitors or glucocorticoid receptor antagonists)
- Bilateral adrenalectomy

- Our pt was started on carboplatin and etoposide chemotherapy during his admission
- In 3 weeks, his repeated 24hrs urinary cortisol was 45 (3.5-45 mcg/24hrs), ACTH 170, cortisol 36.9 at 2PM
- He continued his chemotherapy every 4 weeks with a plan for total of 6 cycles



	21-Jul	15-Aug	26-Sep
cortisol	941	45	14

Follow up:

- Restaging imaging revealed a slight decrease in size of metastatic lesions
- The pt will start brain radiation after his chemotherapy
- Repeat 24hrs urine collection for cortisol Q8 weeks

- What are the most common tumors with ectopic ACTH production
- Survival rate of patients with ectopic ACTH and small cell carcinoma
- Chemotherapy as a tool to control ectopic ACTH?

Tumors related to ectopic ACTH production:

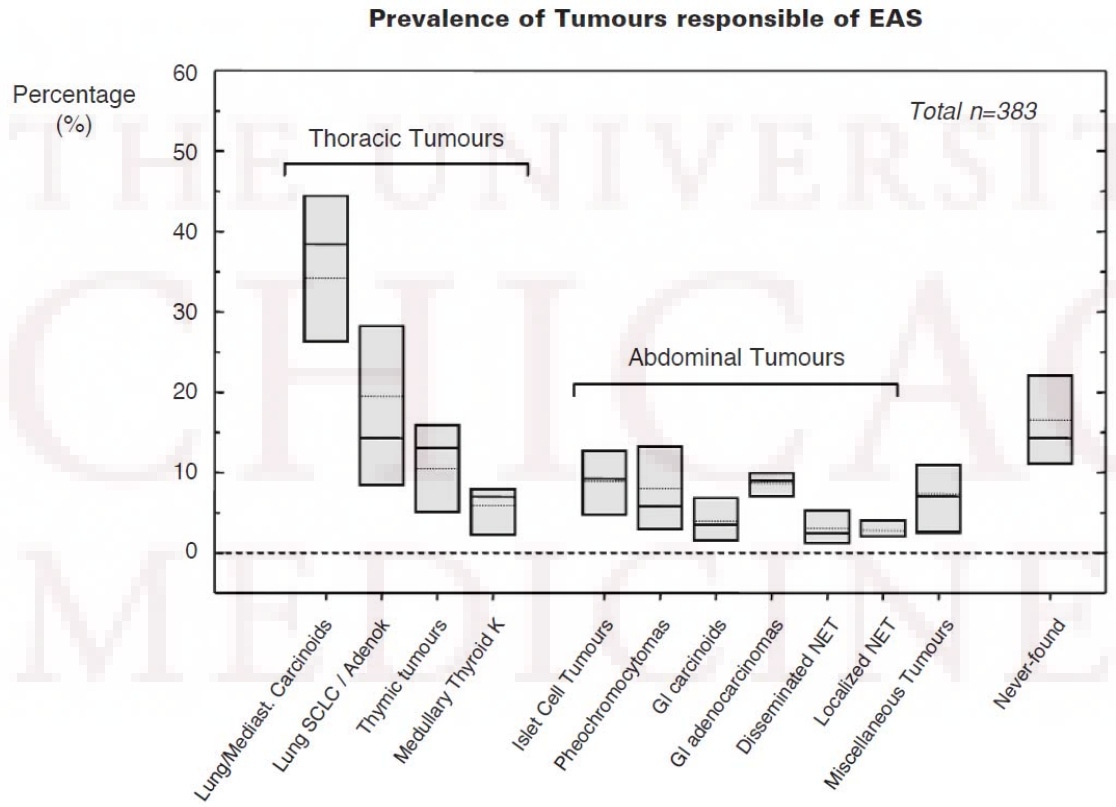


Figure 1. Distribution of the most frequent source (> 2%) of ectopic ACTH secretion in a group of 383 patients with EAS syndrome based on the following published series: Aniszewski et al. (16), Findling et al. (13), Imura et al. (15), Doppman et al. (12), Howlett et al. (14), Ilias et al. (11), Isidori et al. (9), Salgado et al. (17).

Ectopic ACTH syndrome. Isidori AM, Lenzi A. Arq Bras Endocrinol Metabol. 2007 Nov;51(8):1217-25.

Tumors rarely associated with ectopic ACTH:

Table 1. Tumours rarely associated with EAS. The frequency is calculated among all reported cases in literature.

	FREQUENCY 1–3%	FREQUENCY ≤ 1%
Tumours associated with EAS	Ovarian carcinoma	Esophageal carcinoma
	Colonic/anal carcinoma	Kidney tumor
	Prostate	Hepatocarcinoma
	Uterine cervix carcinoma	Breast carcinoma
	Neuroblastoma	Salivary gland tumor
		Mesothelioma
		Lymphoma
	[Ectopic pituitary adenoma]	Melanoma
		Leydig cell tumor
		Larynx carcinoma
		Gallbladder tumours

Ectopic ACTH syndrome. Isidori AM, Lenzi A. Arq Bras Endocrinol Metabol. 2007 Nov;51(8):1217-25.

Small cell cancer and ectopic ACTH:

- Retrospective chart review of 545 patients with SCLC seen at Toronto General Hospital between 1980 and 1990 was done and identified 23 patients (4.5%) with Cushing's syndrome and ectopic ACTH production.
- 17 male and 6 female patients with a median age of 60 years.
- 7 patients had limited disease and 16 had extensive disease at their initial diagnosis of SCLC, but 20 of 23 had extensive disease at the time of diagnosis of Cushing's syndrome.
- All patients were treated with combination of chemotherapy: cyclophosphamide, doxorubicin, and vincristine (CAV) or etoposide (VP-16)-cisplatin (VP-CP).

Cushing's syndrome associated with ectopic corticotropin production and small-cell lung cancer. Shepherd FA, Laskey J, Evans WK, Goss PE, Johansen E, Khamsi F. J Clin Oncol. 1992 Jan;10(1):21-7.

Small cell cancer and ectopic ACTH:

Table 5. Response to Combination Chemotherapy

Response by Time of Presentation of Ectopic ACTH Production	Limited Disease (%)	Extensive Disease (%)	Total (%)
At initial presentation of SCLC			
No. of patients	3	10	13
CR	1 (33)	1 (10)	2 (15)
PR	1 (33)	3 (30)	4 (31)
PD	0	6 (60)	6 (46)
Early death	1 (33)	0	1 (8)
At relapse of SCLC			
No. of patients		10	
No treatment		2 (20)	
CR		0	
PR		3 (30)	
PD		5 (50)	

Abbreviations: CR, complete response; PR, partial response; PD, progressive disease.

- Ketoconazole was used in the treatment of **8 patients**.
- Only in **1 patient** was ketoconazole given without concurrent chemotherapy, and a partial hormone response was achieved.
- **2 of the remaining 7 patients** demonstrated no response, and **1** died before repeat hormone testing was undertaken.
- **4 patients** had partial hormone response even though their tumors did not respond clinically to chemotherapy.

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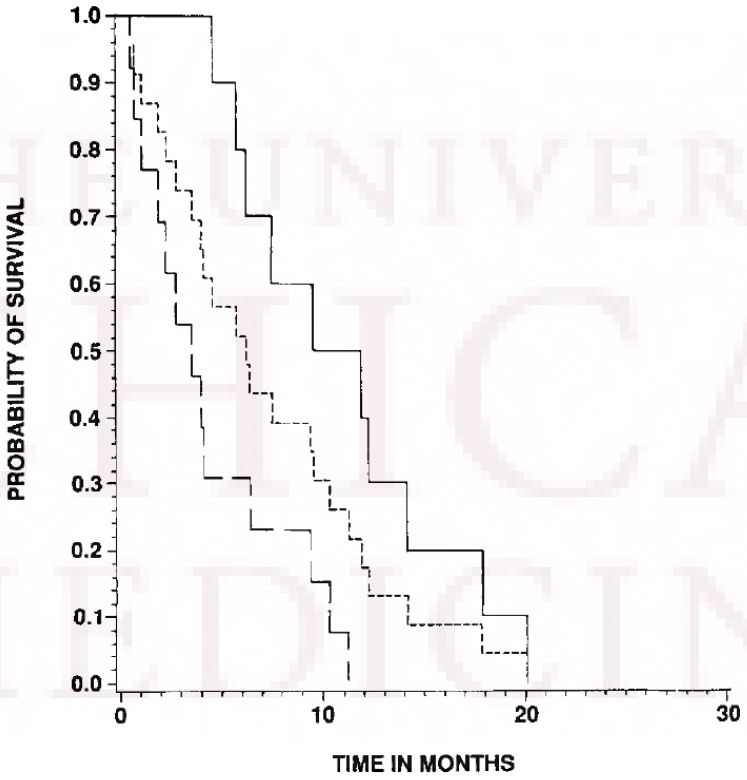

Fig 1. A comparison of the survival from the date of diagnosis of SCLC for patients with ectopic ACTH diagnosed at presentation (— —; n = 13; median survival, 3.57 months) or at relapse (——; n = 10; median survival, 10.7 months) (P = .0020). (----) All patients; n = 23; median survival, 6.23 months.

Cushing's syndrome associated with ectopic corticotropin production and small-cell lung cancer. Shepherd FA, Laskey J, Evans WK, Goss PE, Johansen E, Khamsi F. J Clin Oncol. 1992 Jan;10(1):21-7.

Take home points:

- Ectopic ACTH is a rare etiology of Cushing`s syndrome and accounts for only 12-14% of cases
- Small cell cancer is the second most common cause of ectopic ACTH after carcinoid tumors
- In most of the reported cases of ectopic ACTH with small cell cancer, ketokonazole+chemotherapy was used to control Cushing`s, however few cases report that chemotherapy alone controlled the disease.

References:

- A simplified morning ovine corticotropin-releasing hormone stimulation test for the differential diagnosis of adrenocorticotropin-dependent Cushing's syndrome. Nieman LK, Oldfield EH, Wesley R, Chrousos GP, Loriaux DL, Cutler GB Jr. J Clin Endocrinol Metab. 1993 Nov;77(5):1308-12.
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