57 year-old male with hypokalemia

By Anoopa Koshy, M.D.

Endorama

5/10/2012

HPI

- 57-year-old Bosnian male with a 20 year hx of lung mass (for which he has previously refused worked up) presents to the ER on 3/13 with generalized weakness and found to have hypokalemia (K= 2.7).

- 3 weeks ago, he presented to an OSH with SOB, dyspnea on exertion, and was treated for "a throat infection"

  -K was noted to be as low as 1.7.

  -discharged home on K supplements and antibiotics

- Re-presented to the OSH 5 days prior to admission with DOE/SOB after walking only 10 feet, polyuria, polydipsia, generalized weakness,and a 15-lb weight loss in 2 weeks.

  -left AMA before work-up could be completed

HPI

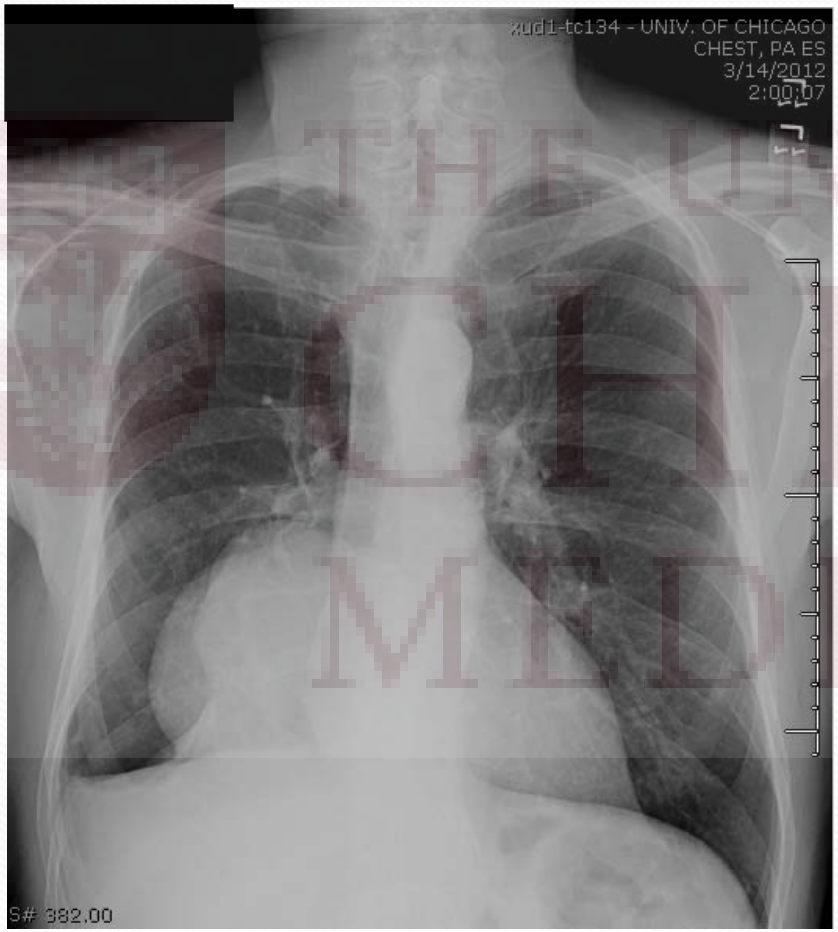
- Progressive, generalized weakness for 3-4 months.
- ~30 lbs of unintentional weight loss over that same time frame, with associated poor appetite
- Reports poor sleep and poor energy
- Has recently noticed polyuria. Denies polydipsia
- Positive vision change in R eye (describes as blurriness, without field defects).
- No HA or numbness.
- No fevers, chills, or sweats
- No CP, cough, pleuritic chest pain, hemoptysis, or wheezes
- No abdominal pain, nausea, vomiting, diarrhea, constipation, or blood in his stools
- No heat/cold intolerance
- He has not noticed any skin changes

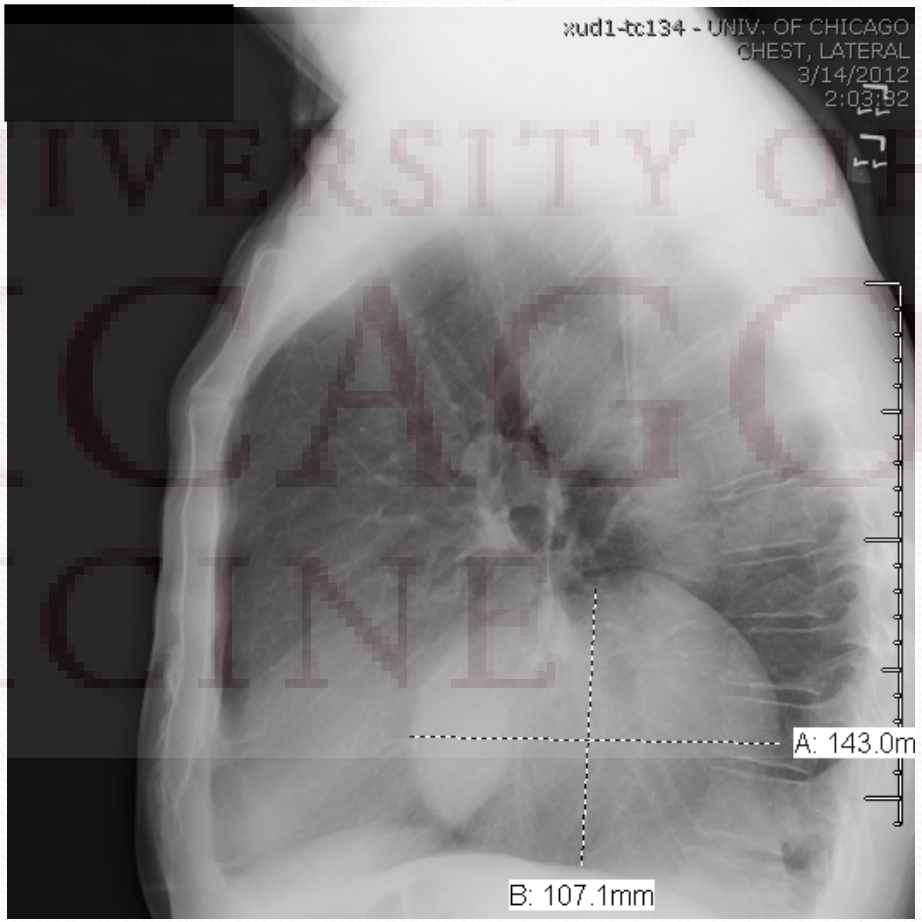
HPI

- Given his reported history of an abnormal CXR and history of lung mass, he was sent for a CXR

- Show image

Chest X-ray



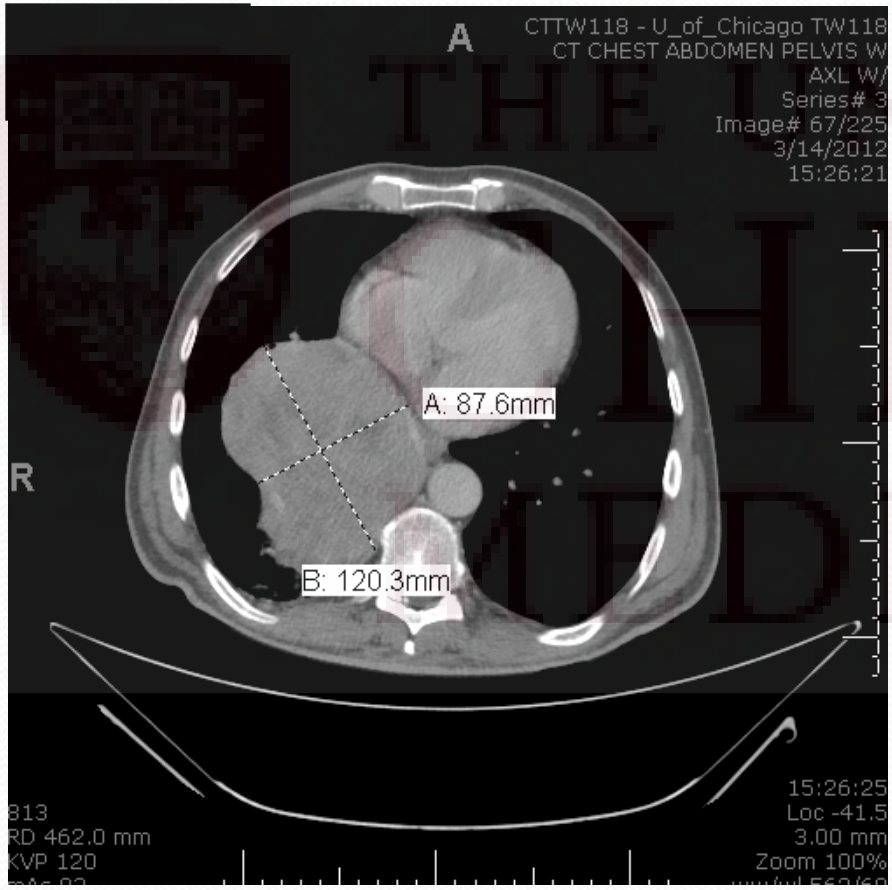


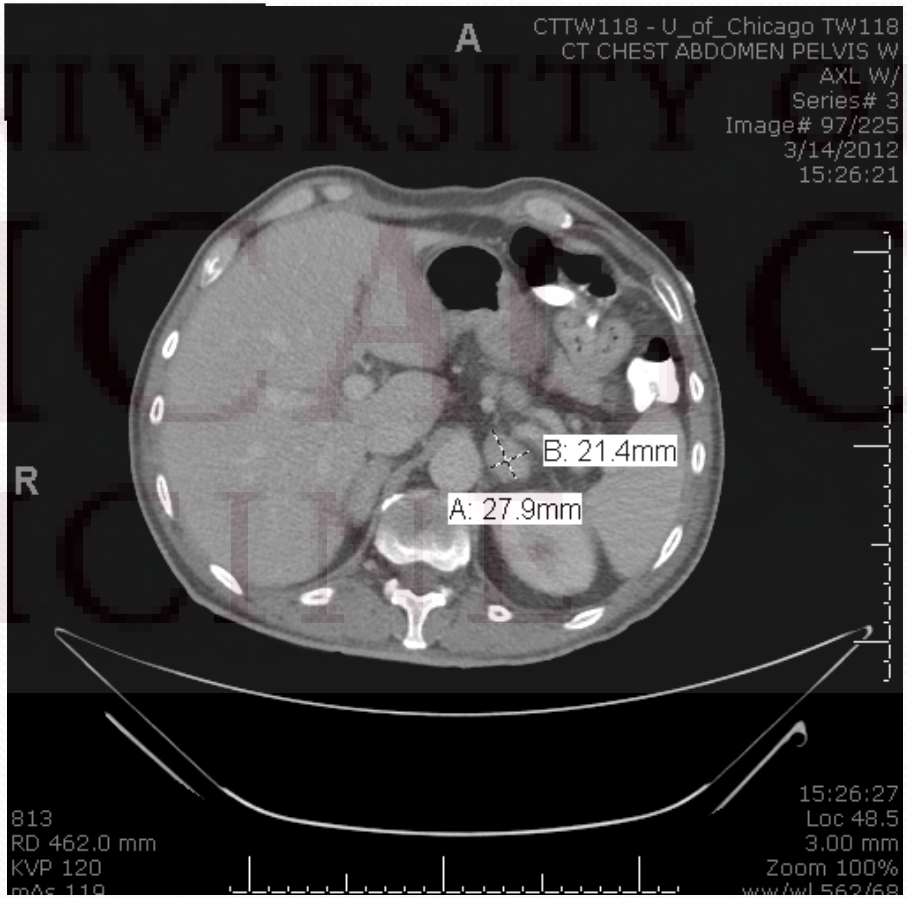
IMPRESSION: Large mass along the right inferior mediastinal border, likely arising from the posterior mediastinum. Small right pleural effusion.

HPI continued…

- Patient admitted to General Medicine for further evaluation of his hypokalemia and his intrathoracic mass.
- Despite aggressive potassium repletion (280 mEq in one 24 hour period), his potassium remained < 3
- CT chest/abdomen/pelvis ordered for further evaluation.

CT chest/abdomen/pelvis





CT chest/abdomen/pelvis: Official Read

1.) There is a 12.0 x 8.8 cm right infrahilar mass with mass effect on the bronchus intermedius and is adjacent to the right pulmonary artery. There is post obstructive atelectasis .

2.) There is a 2.8 x 2.1 cm left adrenal nodule, which may represent adrenal gland thickening. The right adrenal gland appears uniformly hyperplastic.

HPI continued…

- Pulmonary, Oncology, and Thoracic Surgery services consulted for further evaluation of lung mass.
- Random cortisol value from 3/15 returned at 87.3 mcg/d/L at 6:29 AM
- Endocrinology consulted for further evaluation

Past Medical History, Meds

PMHX

- Lung mass x 20 years
- Hypertension
- Depression (recently diagnosed after death of his wife)

Allergies: NDKA

Meds (at discharge from OSH)

Potassium supplement 40 MEQ BID
HCTZ/triamterene
Levaquin
Clindamycin
Megestrol 800 mg daily
Sertraline 50 mg po daily

Social History and Family Hx

SOCIAL HX

- Immigrated from Bosnia in 1998 and worked briefly in retail
- Currently on disability due to lung mass
- Wife died recently in February, 2012
- Denies smoking, EtOH, illicit drugs

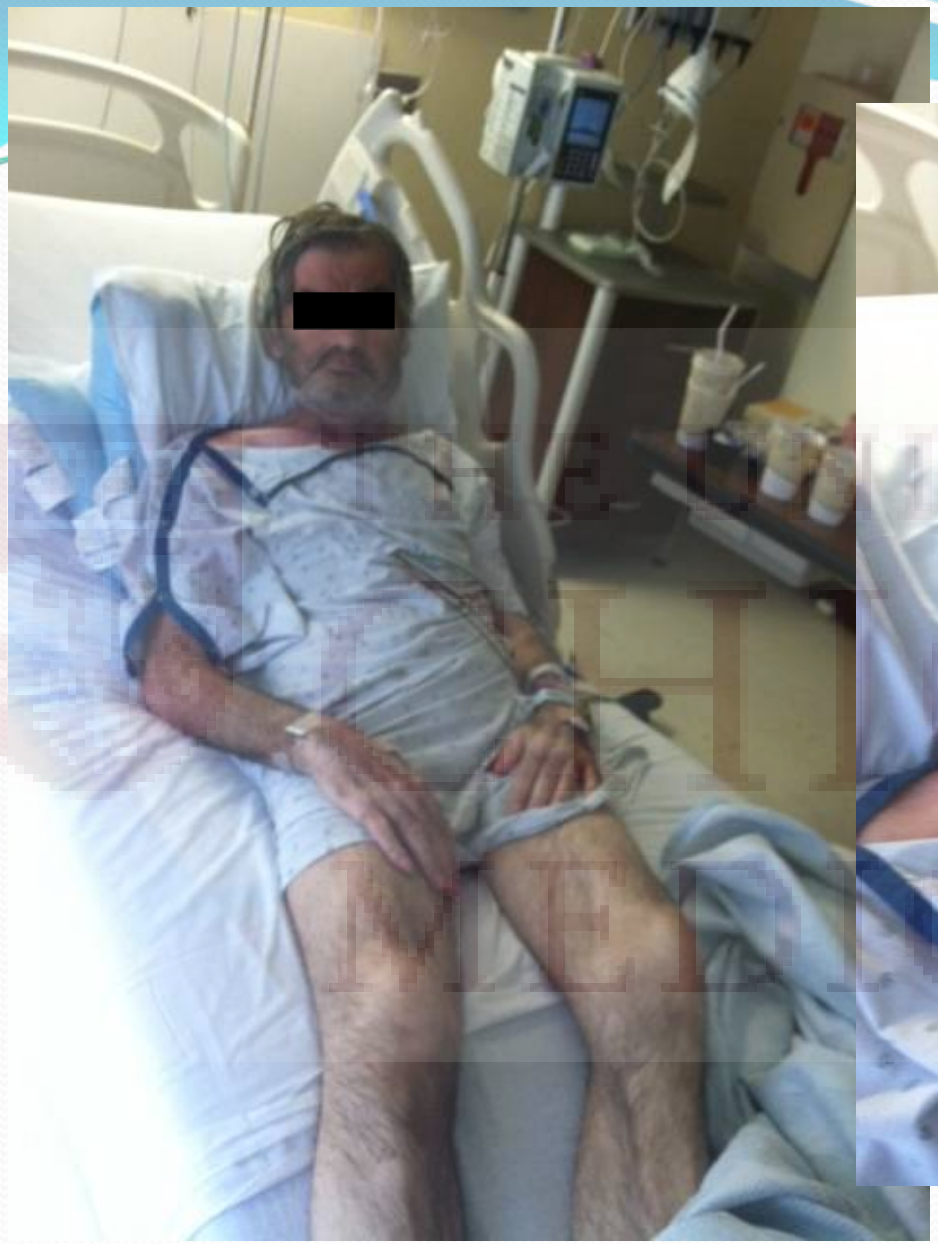
FAMILY HX

No family hx of lung cancer, malignancies, or diabetes

Physical Exam

Vitals: Temp 37.0C BP 154/90 HR 84 RR 12 Sat 93% RA
Weight-160 lbs, Height 6' 1" BMI-21

GEN: Thin, male in NAD
HEENT: Sclerae anicteric. Oropharynx with poor dentition, otherwise clear
NECK: Supple.
CV: RRR. No m/r/g. No JVD. No LE edema. Extremities warm, well perfused.
PULM: Breathing unlabored. Decreased BS with dullness to percussion in the R posterior lung field
ABD: Flat. +BS. Soft. Non-tender. No hepatosplenomegally
EXT: Muscle atrophy in bilateral arms and legs. No edema.
NEURO: A+O X3. CN 2-12 grossly intact. +proximal muscle weakness. Distal sensation intact. Normal finger to nose testing bilaterally. Gait normal bilaterally
SKIN: no rash, no striae, normal pigmentation
PSYCH: Sad affect. Tearful



Labs

3/13/2012 (labs on presentation)

143 | 101 | 8 / 135
2.7 | 28 | 0.6\

3/14/2012
Urine electrolytes: Na 12 mEq/L,
K 33 mEq/L , Cl <20 mEq/L
Aldosterone- <4 ng/dl
Renin- 7.5 ng/ml/hr
Normal (Na deplete): 2.9-10.8
Normal (Na replete): 0.6-3

3/16/2012 at 6:29 AM
ACTH- 311 (<50 pg/dl)
Cortisol- 97.3 mcg/dl
TSH- 0.62 (0.3-4 mcU/ml)

13.9 \ 14.8 / 124
/42.3 \
AST-30
ALT-53
Alk phos-69
Tbili-1.3
Tprotein-5.3
Albumin-3.5

Calcium- 7.5 (8.4-10.2 mg/dl)
Albumin 3.5 (3.5-5 g/dl)
Corrected calcium- 7.9 mg/dl
Magnesium 2 (1.6-2.5 mg/dl)
Phosphorus- 1.9 (2.5-4.4 mg/dl)
PTH- 86 (15-75 pg/ml)
1, 25 OH vit D- 71 (18-64 pg/ml)
25 OH vit D- 8 (10-52 ng/ml)

What are your thoughts and what tests would you order next?

24-hr urine free cortisol

Entry Date

3/20/2012

Component Results

Cortisol, Free, Ur (High):
11640
Reference range: 3.5 to 45
Unit: mcg/24 h
Test Performed or Referred by: Mayo Clinic Dept of Lab Med and Pathology, 200 First Street SW, Rochester, MN 55905

Collection Duration:
24
Urine Volume:
6000
Unit: mL
Test Performed or Referred by: Mayo Clinic Dept of Lab Med and Pathology, 200 First Street SW, Rochester, MN 55905

5-HIAA

Entry Date

3/20/2012

Component Results

5-Hydroxyindoleacetic Acid (High):
18
Reference range: <=8.0
Unit: mg/24 h
In this sample, the excretion of 5HIAA was elevated. This finding could be a pharmacological or dietary artifact (several fruits and vegetables contain large amounts of serotonin, the precursor of 5HIAA), but could also be indicative of the presence of a serotonin-producing tumor.
Test Performed or Referred by: Mayo Clinic Dept of Lab Med and Pathology, 200 First Street SW, Rochester, MN 55905

Collection Duration:
24
Urine Volume:
6000

24-hr urine studies

Component Results

Collection Duration:
24
Urine Volume:
6000
Unit: mL
Test Performed or Referred by: Mayo Clinic Dept of Lab Med and Pathology, 200 First Street SW, Rochester, MN 55905
Norepinephrine:
46
Reference range: 15 to 80
Unit: mcg/24 h
Test Performed or Referred by: Mayo Clinic Dept of Lab Med and Pathology, 200 First Street SW, Rochester, MN 55905
Epinephrine, Ur:
7.2
Reference range: 0.0 to 20.0
Unit: mcg/24 h
Test Performed or Referred by: Mayo Clinic Dept of Lab Med and Pathology, 200 First Street SW, Rochester, MN 55905
Dopamine (High):
1482
Reference range: 65 to 400
Unit: mcg/24 h
Test Performed or Referred by: Mayo Clinic Dept of Lab Med and Pathology, 200 First Street SW, Rochester, MN 55905

Chromogranin A

Component Results

Chromogranin A (High):
2560
Reference range: <=225
Unit: ng/mL
Impaired renal or hepatic function or treatment with proton pump inhibitors may result in artifactual elevations of Chromogranin A.
Test Performed or Referred by: Mayo Clinic Dept of Lab Med and Pathology, 200 First Street SW, Rochester, MN 55905

Endo Recs

- Started Spironolactone at 100 mg po BID, eventually titrated to 200 mg po BID
- Started Amiloride 5 mg po daily, eventually titrated to 10 mg po daily
- Aggressive IV and po K replacement with K checks q6h
- Started ergocalciferol 4,000 units daily and calcium carbonate 1,250 mg QID. Recommended DEXA scan.
- Started lantus 10 units SC daily along with a low dose novolog sliding scale

TABLE 1.

Clinical signs and symptoms of patients with CS caused by known or presumed ectopic ACTH secretion (n = 90)

	n (%)
Muscle weakness	74/90 (82)
Body weight	
Increase	64/90 (70)
Decrease	9/90 (10)
Hypertension	70/90 (78)
Menstrual irregularities or amenorrhea	28/36 (78)
Hirsutism	36/48 (75)
Osteopenia or osteoporosis[1]	27/36 (75)
Hypokalemia	64/90 (71)
Psychiatric disorders	48/90 (53)
Bruising	47/90 (52)
Infections	46/90 (51)
Diabetes	45/90 (50)
Violaceous striae	40/90 (44)
Truncal obesity	35/90 (39)
Edema	34/90 (38)
Body mass index > 28 kg/m^2	32/90 (36)
Fractures[2]	27/90 (30)
Insomnia	26/90 (29)
Libido	
Decrease	21/88 (24)
Increase	1/88 (1)
Impaired cognition or memory	20/90 (22)
Hyperpigmentation	17/90 (19)

Ilias I, Torpy DJ, Pacak K, Mullen N, Wesley RA, Nieman LK 2005 Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health.
J Clin Endocrinol Metab 90:4955–4962.

Hypertension and Hypokalemia in Cushing's Syndrome

- Increased peripheral vascular sensitivity to adrenergic agonists
- Increased hepatic production of renin substrate (angiotensinogen)
- Activation of renal tubular type 1 (mineralocorticoid) receptors by cortisol (due to severe hypercortisolism, which is usually due to ectopic ACTH secretion)
- High serum cortisol concentrations overwhelm the ability of the kidneys to convert cortisol to cortisone, resulting in activation of mineralocorticoid receptors.
- Hypokalemia may also result from adrenal hypersecretion of mineralocorticoids such as deoxycorticosterone and corticosterone.

Bone loss and Glucose intolerance

- **Bone loss**

  - Osteoporosis common in patients with Cushing's syndrome

  -caused by decreased intestinal calcium absorption

  -decreased bone formation

  -increased bone resorption

  - decreased renal calcium reabsorption

- **Glucose intolerance**

  - common in Cushing's syndrome

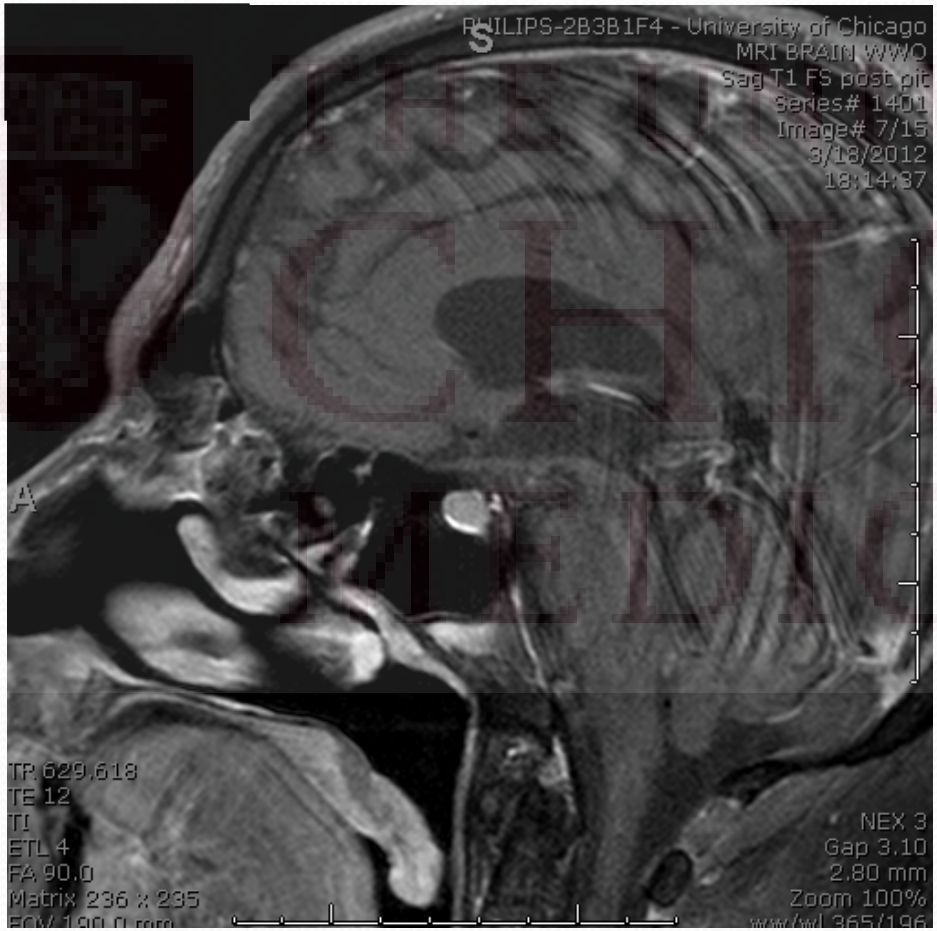
  -primarily due to stimulation of gluconeogenesis by cortisol and peripheral insulin resistance caused by obesity

  - direct suppression of insulin release also may contribute

Neuropsychological changes and cognition

- Emotional lability
- Agitated depression
- Irritability
- Anxiety
- Panic attacks
- Mild paranoia
- Insomnia
- Depression (occurs in 2/3 of patients with Cushing's syndrome)

MRI pituitary



IMPRESSION:

1. Normal appearance of the pituitary gland and hypothalamic region.

2. Multifocal abnormal signal intensity within the subcortical and periventricular white matter, nonspecific however most likely represents chronic small vessel ischemic disease.

- What would you do next?

CRH Stimulation Test

Time (min)	-15	0	15	30	60	90	120	180
ACTH	373	420	445	435	386	273	401	431
Cortisol	114	113	112	110	113		115	113

Summary of findings

- The urinary cortisol in excess of >11,000 ug/24 hr is extraordinary, and is diagnostic of Cushing's syndrome.
- The diagnosis of ectopic ACTH Syndrome is confirmatory with the results of the CRF stimulation test (elevated cortisol and ACTH unresponsive to CRH stimulation).
- The high 5-HIAA and dopamine levels are consistent with an active neuroendocrine tumor.

TABLE 3.

Causes of ectopic ACTH secretion from literature data (Refs. 54 55 56 57 58)

Localization	Frequency, % (No.)			
		Aniszewski et al., 2001 (54)	Ilias et al., 2005 (55)	Isidori et al., 2005 (56)
Bronchial carcinoid	25% (26/106)	40% (35/90)	34% (12/35)	40% (10/25)
Pancreatic carcinoid	16% (17/106)	1% (1/90)	8% (3/35)	12% (3/25)
Small-cell lung cancer[1]	11% (12/106)	3% (3/90)	6% (2/35)	ND
Thymic carcinoid	5% (5/106)	5% (5/90)	6% (2/35)	16% (4/25)
Unknown/occult	7% (7/106)	19% (17/90)	14% (5/35)	8% (2/25)
Other	36% (39/106)	32% (27/90)	32% (11/35)	24% (6/25)

Pulmonary carcinoid tumors

- Account for 25% of neuroendocrine tumors, but only 1% of lung cancers
- Arise from enterochromaffin cells (a bronchial mucosal cell that is part of the Diffuse Neuroendocrine System, or DNES)
- Presentation: usually present with pulmonary symptoms (obstructive pneumonia, cough, wheeze, hemoptysis)
  - Carcinoid syndrome is rare
  - 25-30% of patients are asymptomatic (found incidentally or post-mortem)
- Imaging
  - Characteristic CT imaging findings: well defined, centrally located tumors involving the airway with calcification
  - Roles for other imaging studies (PET, MRI, somatostatin receptor scintigraphy) are not well defined.
- Pathology
  - Can be broken down into typical and atypical carcinoids based off histologic appearance

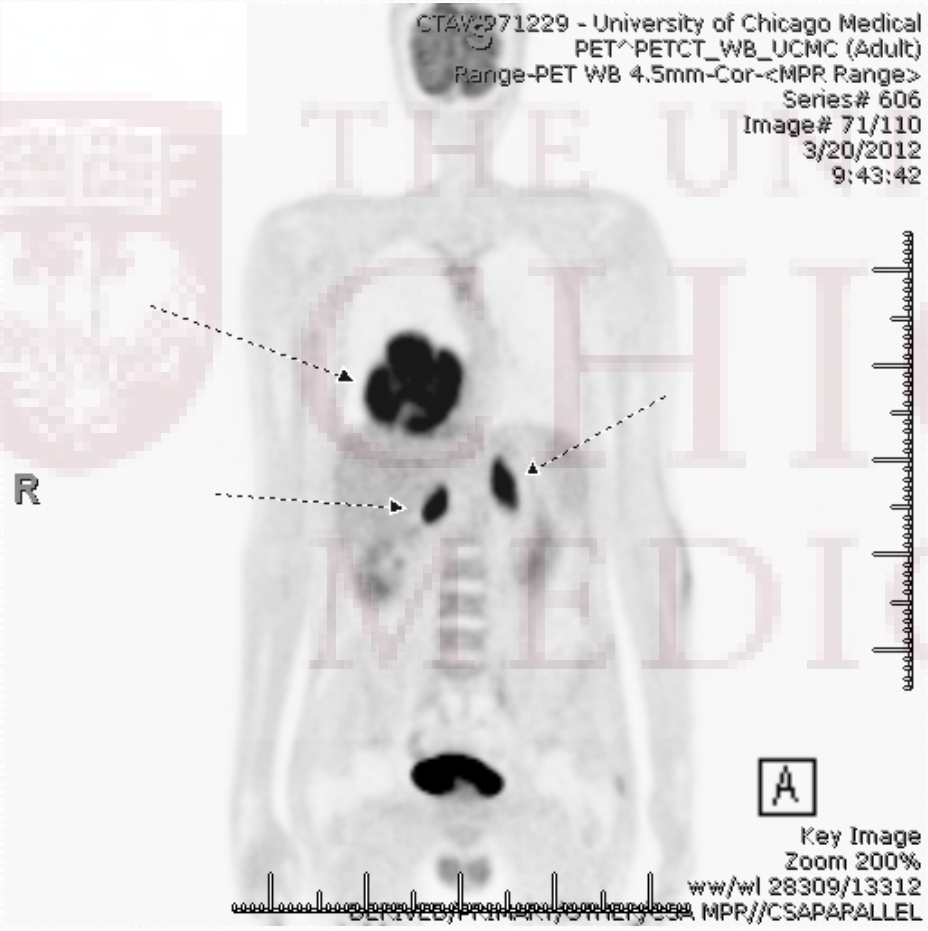
Pulmonary carcinoid tumors

- Staging
  - Follows TNM guidelines used for other NSCLCs
  - Can spread to regional nodes, bone, adrenal glands, liver, and brain
  - Atypical carcinoids at higher risk of metastasis than typical carcinoids (one series shows 25% of pts developing distant disease)
- Prognosis
  - Variably reported, ranging from 5 year surival of 44-97%
  - Dependent on histologic subtype and stage of disease at presentation
- Treatment
  - Surgery is treatment of choice and only curative option
  - For patients with unresectable or metastatic disease, there is currently limited data regarding chemotherapy or XRT
  - Regimens previously reported: interferon alpha, etoposide based regimens, streptozocin, 5-FU, octreotide (if carcinoid syndrome)
  - Under study: VEGF inhibitors, mTOR inhibitors, tyrosine kinase inhibitors

Clinical Course continued…

- Thoracic Surgery requests whole body PET scan prior to surgical removal of lung mass

PET Scan



- Markedly hypermetabolic large R infrahilar pulmonary mass (SUV max 15.2), compatible with tumor activity.
- Both enlarged adrenal glands are hypermetabolic (SUV max 14.1). This is suspicious for tumor involvement, or alternatively could represent benign uptake from marked bilateral adrenal hyperplasia
- No FDG avid tumor elsewhere

Adrenal mets versus hyperplasia?

- Thoracic surgery reluctant to operate given PET scan results.
- Is the intense uptake in the adrenal glands evidence of metastatic disease?
- Intense bilateral uptake would be unusual for mets
- The CT scan of the adrenals suggest bilateral hyperplasia (as one would expect in ectopic ACTH syndrome)
- 2 papers indicate that SUVmax in adrenal hyperplasia can be 3.5-5.5 (metastatic disease is usually >3.1 also):
- We recommended surgical removal of lung mass

Surgery

- He underwent a right thoracotomy and pneumonectomy on 3/27 by Dr. Ferguson.
- No complications with surgery
- Extubated without difficulties
- After surgery, he was monitored closely for adrenal insufficiency with q2h cortisol checks for 24 hours
- Did not develop overt clinical or biochemical signs of adrenal insufficiency.

ACTH and Cortisol Trend After Surgery

Hide data prior to: 3/13/2012 Use Date Range Wizard

	15 3/15/2012 0629	14 3/27/2012 1549	13 3/27/2012 1810	12 3/27/2012 2000	11 3/27/2012 2214	10 3/27/2012 2359	9 3/28/2012 0200	8 3/28/2012 0400	7 3/28/2012 0600
ENDOCRINOLOGY									
Cortisol	87.3 *	101.9 *	57.6 *	34.4 *	37.5 *	26.4 *	24.8 *	23.5 *	24.9 *
ACTH	311.0 !	34.8	26.6	22.0	15.0	24.5	23.7	48.5	47.4

Surgery

Hide data prio

	6 3/28/2012 0810	5 3/28/2012 1248	4 3/28/2012 2027	3 3/29/2012	2 3/29/2012 0617
ENDOCRINOLOGY					
Cortisol	28.7 *	29.9 *	21.1 *	16.0 *	24.3 *
ACTH	60.7 !	43.3		43.0	37.0

Hydrocortisone 20 mg/10 mg started

Clinical Course

- He was discharged home on hydrocortisone 20 mg PO q am, 10 mg PO q afternoon until further follow-up.
- His potassium remained normal without supplementation.
- His blood sugars normalized and his insulin was stopped.

Post-op 24-hr urine free cortisol

Entry Date

4/2/2012

Component Results

Cortisol, Free, Ur (High):
163
Reference range: 3.5 to 45
Unit: mcg/24 h
Test Performed or Referred by: Mayo Clinic Dept of Lab Med and Pathology, 200 First Street SW, Rochester, MN 55905

Collection Duration:
24

Urine Volume:
4650

Note: 24 hour urine cortisol down from 11,640 mcg prior to surgery (nl < 35)

Post-op 5-HIAA

Entry Date

4/3/2012

Component Results

5-Hydroxyindoleacetic Acid:
3.7
Reference range: <=8.0
Unit: mg/24 h
Test Performed or Referred by: Mayo Clinic Dept of Lab Med and Pathology, 200 First Street SW, Rochester, MN 55905

Collection Duration:
24

Urine Volume:
4650

Note: 24 hour urine 5-hydroxyindoleacetic Acid down from 18 mg prior to surgery (nl < 8)

Post-op Dopamine

Entry Date

4/2/2012

Component Results

Collection Duration:
24
Urine Volume:
4650
Norepinephrine:
65
Reference range: 15 to 80
Unit: mcg/24 h
Test Performed or Referred by: Mayo Clinic Dept of Lab Med and Pathology, 200 First Street SW, Rochester, MN 55905
Epinephrine, Ur:
4.7
Reference range: 0.0 to 20.0
Unit: mcg/24 h
Test Performed or Referred by: Mayo Clinic Dept of Lab Med and Pathology, 200 First Street SW, Rochester, MN 55905
Dopamine:
79
Reference range: 65 to 400
Unit: mcg/24 h
Test Performed or Referred by: Mayo Clinic Dept of Lab Med and Pathology, 200 First Street SW, Rochester, MN 55905

Note: 24 hour urine dopamine down from 1482 mcg prior to surgery (nl 65-400)

Pathology

- Invite Dr. Li to present pathology findings.

Additional Questions

- Why was the staining for ACTH negative?
- Could there have been ectopic CRH production?

A Case Report

A 56 year old woman presented with clinical and laboratory features consistent with ACTH-dependent CS.

- Pituitary imaging was normal and cortisol did not suppress with a high dose dexamethasone test, consistent with a diagnosis of ectopic ACTH.
- CT imaging did not reveal any discrete lung lesions but there were mediastinal and abdominal lymphadenopathy and multiple liver lesions suspicious for metastatic disease.
- Laboratory testing was positive for elevated serum carcinoembryonic antigen and chromogranin A.
- Serum markers of carcinoid, medullary thyroid carcinoma, and pheochromocytoma were in the normal range. Because the primary tumor could not be identified by imaging, biopsy of the presumed metastatic liver lesions was performed.
- Immunohistochemistry was consistent with a neuroendocrine tumor, specifically small cell carcinoma.
- Immunostaining for ACTH was negative but was strongly positive for CRH and laboratory testing revealed a plasma CRH of 10 pg/ml (normal 0 to 10 pg/ml) which should have been suppressed in the presence of high cortisol.

CONCLUSIONS:

- This case illustrates the importance of considering the ectopic production of CRH in the differential diagnosis for presentations of ACTH-dependent Cushing's Syndrome.

Shahani S, Nudelman RJ, Nalini R, Kim HS, Samson SL. Ectopic corticotropin-releasing hormone (CRH) syndrome from metastatic small cell carcinoma: a case report and review of the literature. Diagn Pathol. 2010 Aug 31; 5:56.

From: Diagn Pathol. 2010; 5: 56.
Published online 2010 August 31. doi: 10.1186/1746-1596-5-56

Table 2

CRH Positive and ACTH negative Tumors causing Cushing's Syndrome

NEOPLASM	% of CASES (n = 21)	REFERENCES
Medullary Thyroid Cancer	33	[8,9,11,15,18]
Pheochromocytoma	19	[10,11,13,16]
Prostate Cancer	14	[9,17]
Small Cell Lung Carcinoma	9.5	[14,17]
Small Cell Carcinoma (occult primary)[1]	9.5	[14]
Carcinoid	5	[14]
Other	< 10	[14,9]

Shahani S, Nudelman RJ, Nalini R, Kim HS, Samson SL. Ectopic corticotropin-releasing hormone (CRH) syndrome from metastatic small cell carcinoma: a case report and review of the literature. Diagn Pathol. 2010 Aug 31; 5:56.

Outpatient Follow-up

- Patient failed to show-up for his Endocrinology appointment after discharge.
- Had f/u with Thoracic Surgery on 4/20
- Is still taking HC 20/10 mg
- Random cortisol at 16:15 returned at 21.7 mcg/dl and ACTH of 29.5 pg/ml
- Chromogranin A level returned at 170 (nl <225 ng/ml, previously 2560 ng/ml)
- Recommended follow-up with Dr. Salgia in Oncology, has scheduled appointment on 5/11.

Take Home Points

1. Cushing's syndrome should be on the differential for a patient presenting with refractory hypokalemia.

2. The CRH stim test can be used to differentiate pituitary from ectopic ACTH secretion in Cushing's syndrome.

3. Ectopic CRH production can be a cause of Cushing's syndrome, although rare.

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- 7. Ilias I, Torpy DJ, Pacak K, Mullen N, Wesley RA, Nieman LK 2005 Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. J Clin Endocrinol Metab 90:4955–4962.

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8. Susan G. Coe, Winston W. Tan, and Thomas P. Fox. Cushing's Syndrome Due to Ectopic Adrenocorticotropic Hormone Production Secondary to Hepatic Carcinoid: Diagnosis, Treatment, and Improved Quality of Life. J Gen Intern Med. 2008 June; 23(6): 875–878.

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