33 year old women with Cushing's Syndrome

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Endorama

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But first, an ESAP question:

- 73 yo woman is referred to you for management of Cushings. Four months ago, she gained 30 lb and developed severe hyperglycemia, progressive edema, and muscle weakness.
- Exam is notable for BMI 46.2, facial fullness, supraclavicular and dorsocervical fat, ecchymoses, severe proximal muscle weakness, massive peripheral edema.
- Labs notable for K 2.3, urinary free cortisol 3220 ug/24 hr, cortisol 37 ug/dL after 1 mg dex, ACTH 144 pg/mL.
- Pituitary MRI nl, IPSS show no central to peripheral gradient. CT torso, PET, and octreotide scan are nl except for 2 vertebral fxs.
- Two weeks later, you refer her to an endocrine surgeon for bilateral adrenalectomy. At the surgeon's clinic, AM cortisol is 102 ug/dL, K 1.9, glu 303; he would like her to be more medically stable before surgery.
- She is transferred to ICU and started on insulin gtt, LMWH, potassium, spironolactone, and epoetin alfa.

But first, an ESAP question:

- Which of the following medications would you recommend to treat her hypercortisolism and prevent short-term comorbidity?
  - Octreotide and cabergoline
  - Etomidate and trimethoprim-sulfamethoxazole
  - Mitotane and alendronate
  - Ketoconazole and prednisone
  - Mifepristone and dapsone

History of Present Illness

- 33 yo Korean woman with polycystic kidney disease who was admitted to the MICU for hematochezia.
  - Recently diagnosed with Cushing's syndrome.

Past Medical History

- Polycystic kidney disease
  - Mother has PCKD, underwent kidney transplant.
- Nephrolithiasis
  - 1 episode at age 22.

Prior History

- Previously healthy.
- March 2013:
  - Presented to ED for pedal edema, facial fullness, proximal weakness, and hirsutism on the upper lip.
  - Found to have HTN, elevated potassium in the urine.
  - 24 hour urine collection with elevated cortisol levels.
- April 2013:
  - Presented to ED with worsening pedal edema, malaise.
  - Admitted to OSH psychiatric ward for depression.

OSH psychiatric hospitalization

- Random serum cortisol:
  - 98.8 mcg/dL
- Salivary cortisol (nl <4.3):
  - 760.4 nmol/L
  - 553.8 nmol/L
- Midnight serum cortisol:
  - 136.3 mcg/dL
- 1mg dexamethasone suppression test:
  - Cortisol 116 mcg/dL

145 107 66 172

3.1 28 1.8

AST 22, ALT 35, alk phos 97, TB 0.3, alb 2.5

9.7

9.3 107

30.2

- POC glucoses: 150-285
- A1c 7.0%.

OSH MRI Imaging

- MRI pituitary:
  - Normal pituitary
  - 1.9 cm meningioma in the R parietal region.
- Octreotide scan:
  - Normal distribution of activity in the liver, spleen, and lung.
  - Multiple defects in the kidneys.
  - No focal uptake in the adrenal gland.
  - No evidence of pituitary lesion.

Prior History

- May 2013:
  - Presented to ED after being found unconscious with bloody emesis.
  - Hospitalized for 6 weeks, where found to be anemic to Hgb 3.1, thrombocytopenic to plt 58.
  - CT abdomen/pelvis noted diffusely thick adrenal glands.
  - Discharged 10 days prior to admission here.

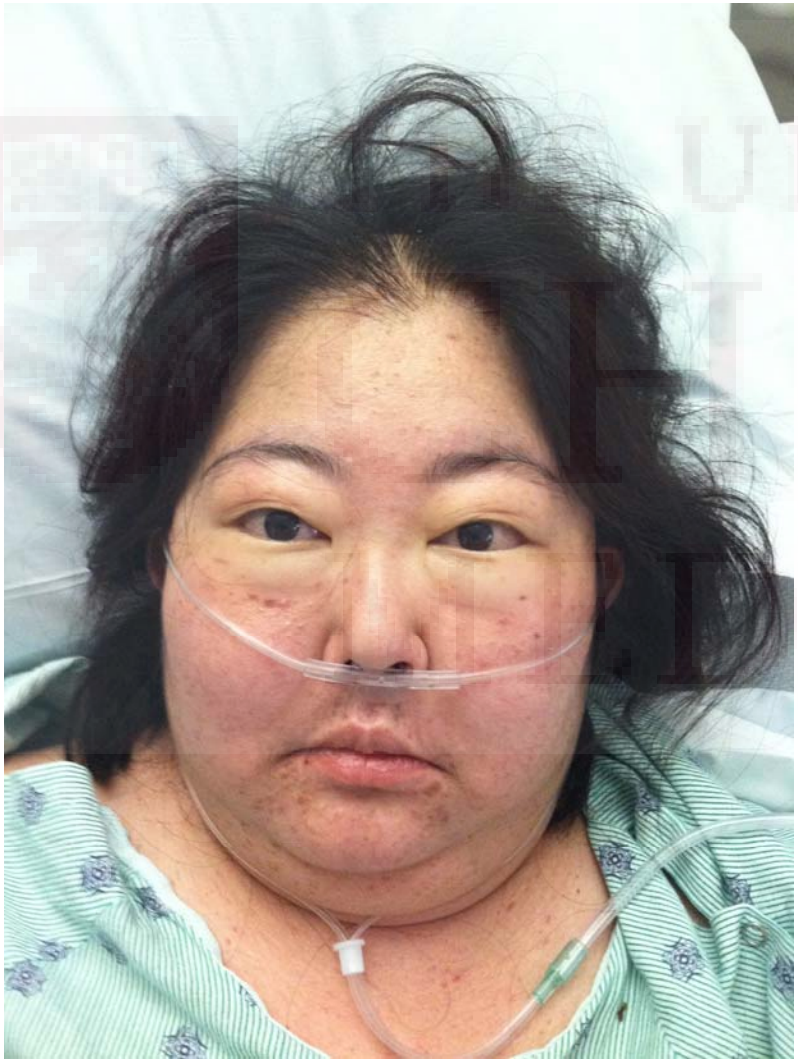
History

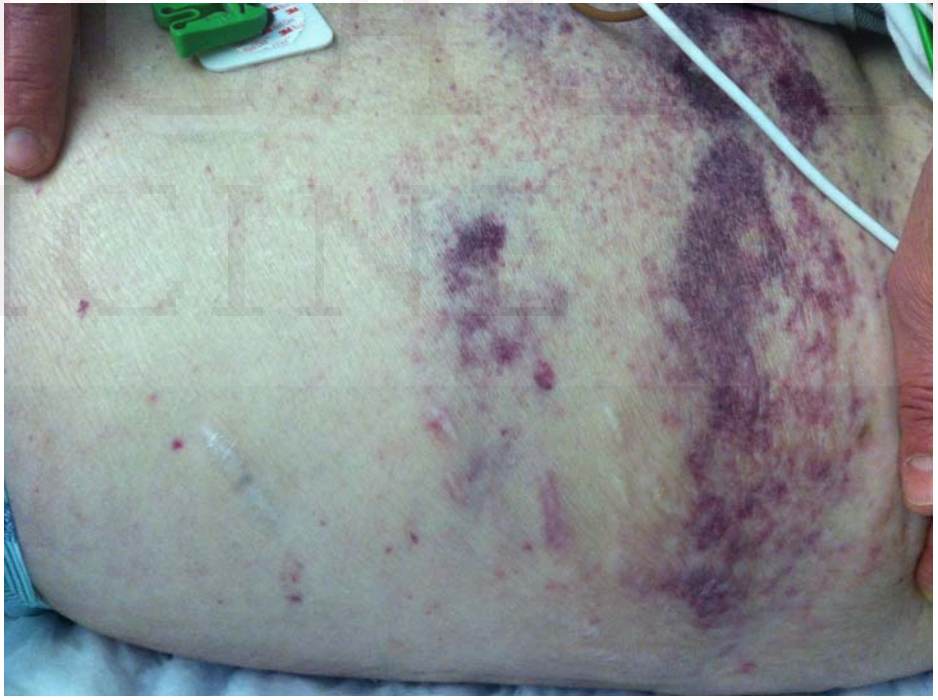
- Medications:
  - Pantoprazole
  - Clonidine
  - Metoprolol
  - Nifedipine
  - 70/30
- Family history:
  - Mother with PCKD, developed diabetes post-transplant.
- Social History:
  - Lives with her mother and brother.
  - Was college bound until her mother had her kidney transplant.
  - No tobacco, etoh use.

ROS

- Constitutional: **Originally gained weight** but recently lost weight. No fevers, chills.
- Respiratory: No shortness of breath, cough.
- Cardiovascular: No chest pain, palpitations.
- Gastrointestinal: Hematochezia but no nausea, vomiting, abdominal pain, diarrhea.
- Genitourinary: **Regular menses** every 6 weeks; LMP 1 month ago.
- Musculoskeletal: **Bedbound**.
- Skin: **Petechial rash**.
- Heme: **Easy bruising**.
- Neurological: No headache. **Extreme muscle weakness**.

Physical Exam





Physical Exam

- Vital signs: BP 156/84, pulse 85, RR 31, T 98.1, wt 165 lb, ht 5’5’’, BMI 27.5
- Constitutional: Appears chronically ill, in no acute distress. Moon facies, acne, mild facial hair on upper lip. Supraclavicular fullness. Buffalo hump.
- Eyes: Conjunctivae are not injected. Sclerae anicteric. Pupils are equal, round, and reactive to light. Extraocular movements are intact.
- ENT: Mucous membranes moist. +thrush.
- 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: Few violaceous striae. Normoactive bowel sounds. Soft, nontender, nondistended.
- Musculoskeletal/extremities: + peripheral edema.
- Neurological: Normal deep tendon reflexes. Muscle strength 2/5 in BLEs and 3/5 in BUEs.
- Skin: Acanthosis nigrans noted. Petechial rash. Diffuse ecchymoses.
- Psychiatric: Normal mood and affect.

Labs

138 102 107

2.8 18 2.1

215

Ca 8.2

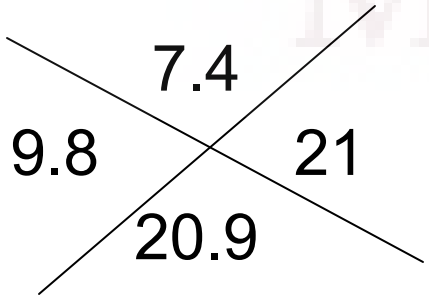
Total protein 5.3, Albumin 2.4

AST 21, ALT 27

Alk phos 99, Total bili 0.1

8AM Cortisol 256.7

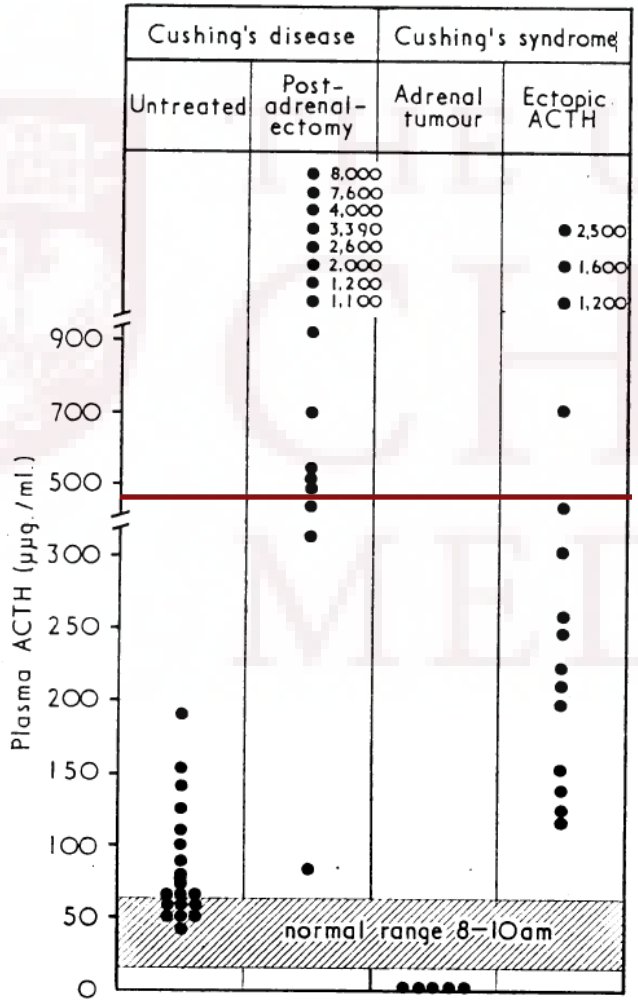
TSH 0.31



Assessment & Plan

- 33 yo woman with PMHx sig. for polycystic kidney disease, recently diagnosed Cushing's Disease, severe anemia and thrombocytopenia who was admitted to the MICU for hematochezia.
- Hypercortisolism: *ACTH is pending.*
  - Acuity of her symptoms, HTN and hypokalemia, extremely high levels of cortisol, and bilateral adrenal enlargement suggests ectopic ACTH.
  - If the ACTH is >200, then it is most likely an ectopic source.
  - If the ACTH is equivocal, would recommend CRH stim test.
  - Obtain baseline 24 hour urine free cortisol.
  - After this is obtained, please start ketoconazole at 200 mg BID.

Why ACTH of 200?



- Plasma ACTH levels in 56 patients with Cushing's.

ACTH 442 pg/mL

Bessler et al. Br Med J. 1968 Nov 30;4(5630):552-4.

Not convinced?

- 8/3: Low dose dexamethasone suppression test
  - Cortisol 83.8 (but received HC 20 mg IV at 5AM)
  - ACTH 36.2
- 8/5: High dose dexamethasone suppression test
  - Cortisol 36.4 (last dose of hydrocortisone on 8/4 at 12:30PM)
  - ACTH 109.0

High dose dexamethasone suppression test

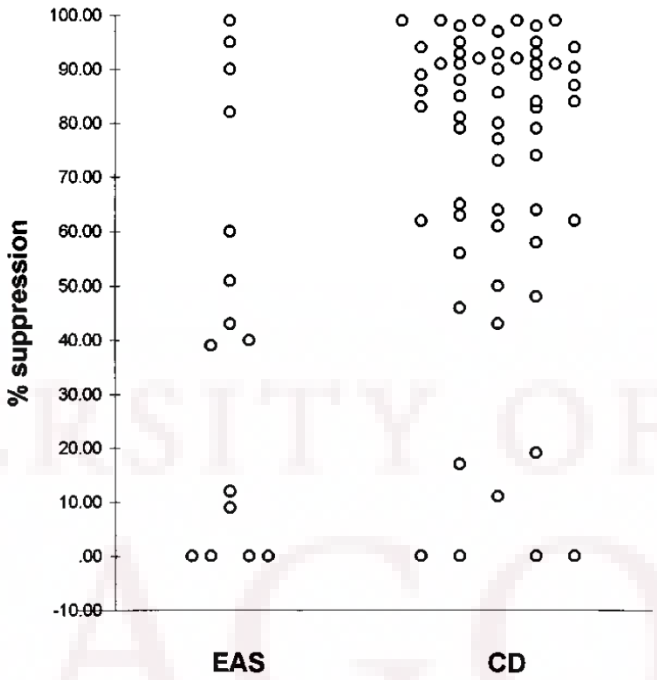


TABLE 3. Logistic regression modeling of probability of Cushing's disease

Model no.	Variables	Patients who underwent high dose dexamethasone test		
		Sensitivity	Specificity	Diagnostic accuracy
1	Age, sex, duration, hypokalemia, urinary free cortisol, plasma ACTH, suppression by ≥50%	100	80	95.6
2	Age, sex, duration, hypokalemia, urinary free cortisol, plasma ACTH, % suppression	98.1	80	94.1
3	Age, sex, duration, hypokalemia, urine free cortisol, plasma ACTH	98.1	78.3	92.7
4	Duration, hypokalemia, plasma ACTH	98.1	66.7	91.2
5	Suppression by ≥50%	79.3	66.7	76.5
6	% Suppression	92.5	26.7	77.9

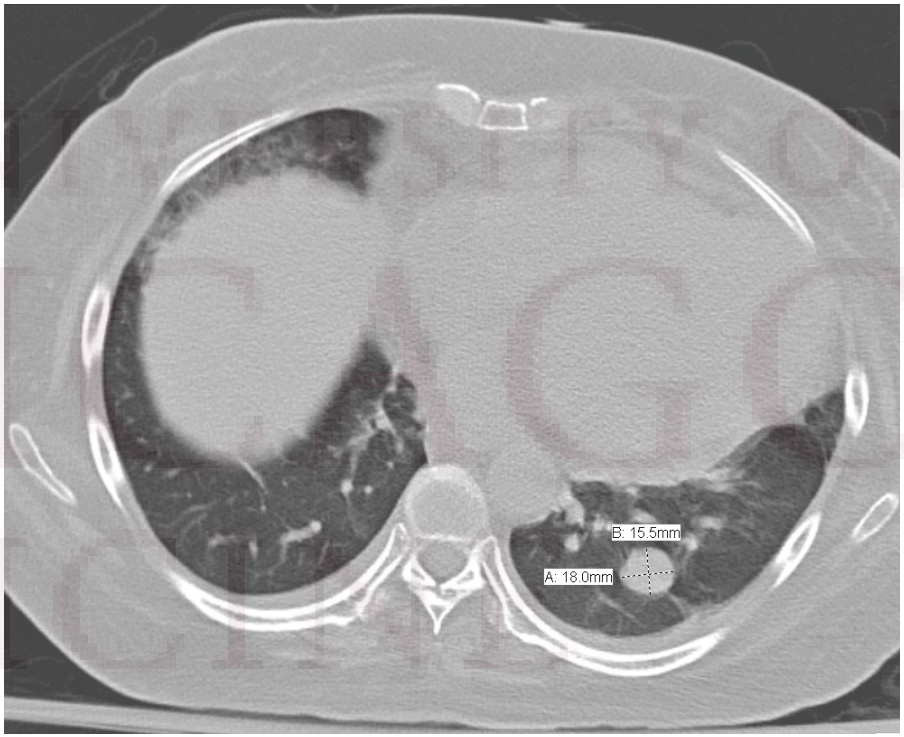
Aron et al. J Clin Endocrinol Metab. 1997 Jun;82(6):1780-5.

Other labs

- Baseline 24 hour urine free cortisol: 1183 mcg/24 hr (nl 3.5 to 45)
- CRH 2.8 pg/mL (nl <10)
- Chromogranin A 1269 ng/mL (nl <93)

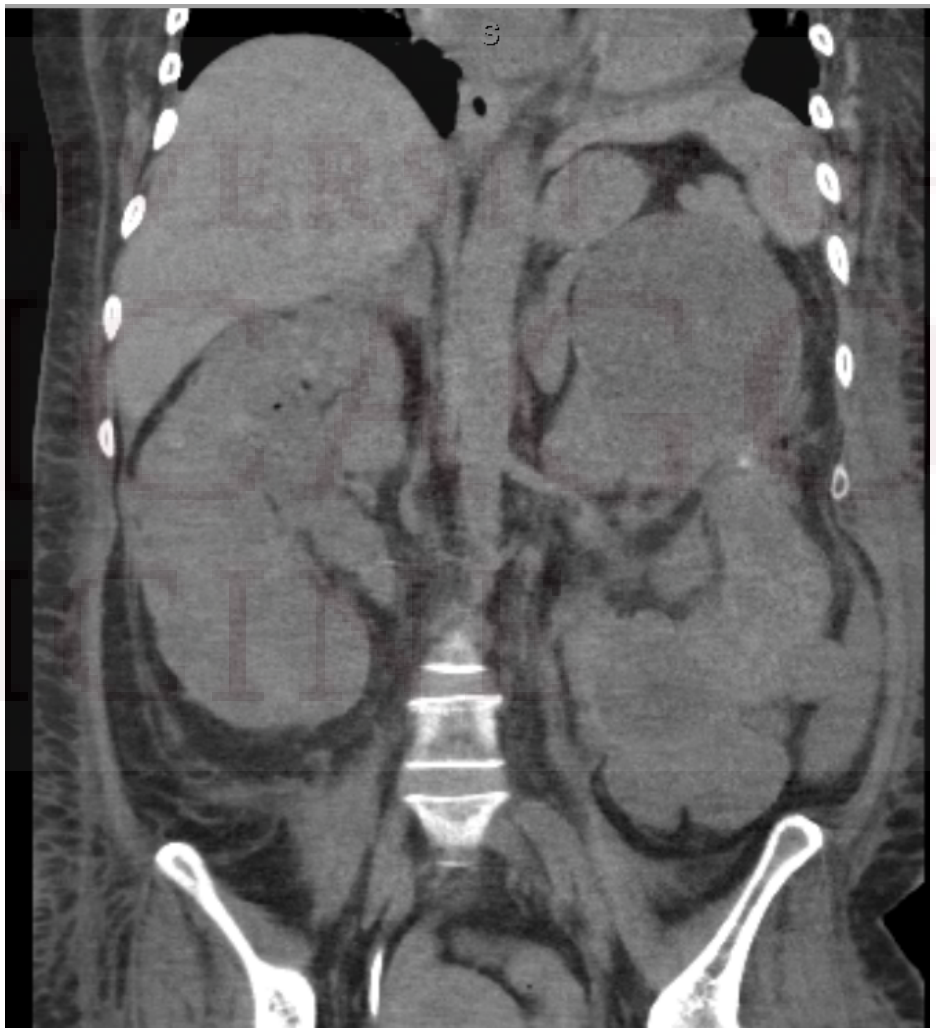
So it's ectopic? Where's it coming from?

- CT chest:
  - Upper lobe predominant reticular ground glass opacities.
  - Well-defined nodule is seen in the left lower lobe measuring 18 x 16 mm.



So it's ectopic? Where's it coming from?

- CT abdomen:
  - Diffusely thickened and enlarged adrenal glands.
  - Markedly enlarged kidneys with complex cysts, cannot exclude underlying solid mass.



Imaging Modalities

- CT scan:
  - 17 pts with ectopic Cushings.
    - Initial CT localized 12 cases, follow up CT localized 3 more.
    - Source was identified in last 2 patients by Gallium DOTA-octretotate.
- Octreotide scan:
  - 6 pts with histologically confirmed bronchial carcinoids.
    - Correctly localized in 3 patients, remaining became positive after 8, 22, and 27 mos of follow up.
    - 2 patients had negative CT scans.
    - No false positives.

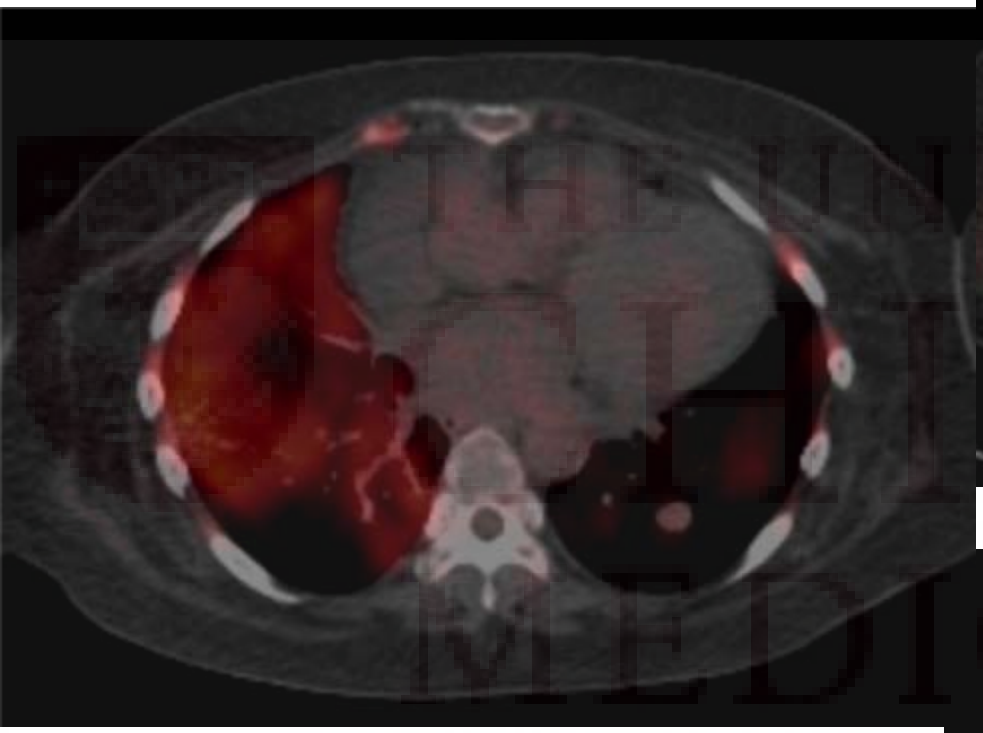
Kakade et al. Endocr Pract. 2013 Sep 6:1-22.
Tsagarakis et al. J Clin Endocrinol Metab. 2003 Oct;88(10):4754-8.

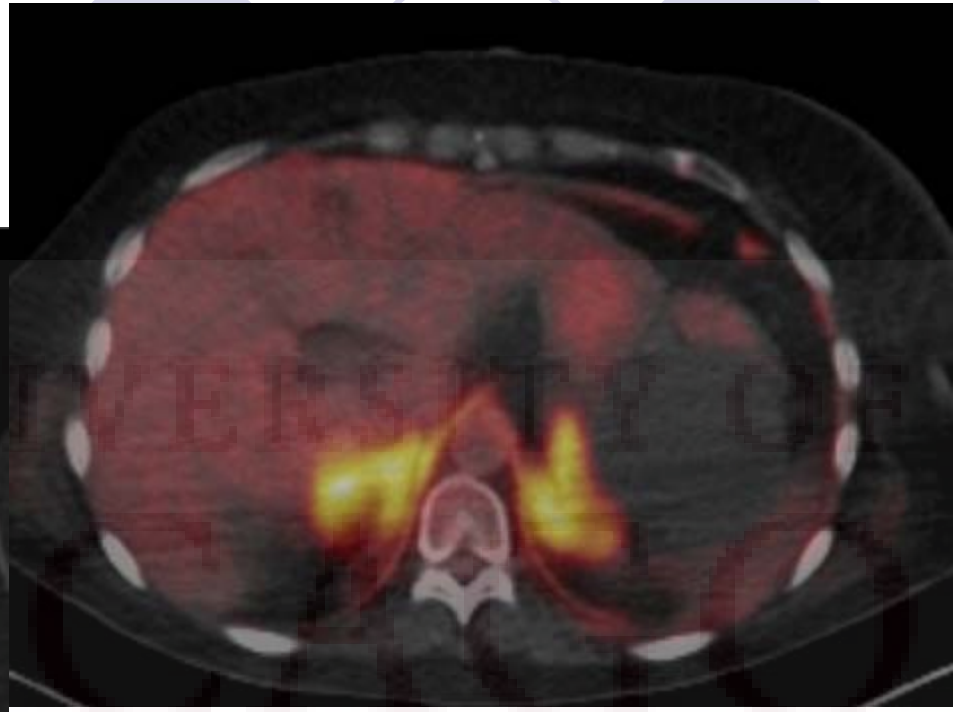
Imaging Modalities

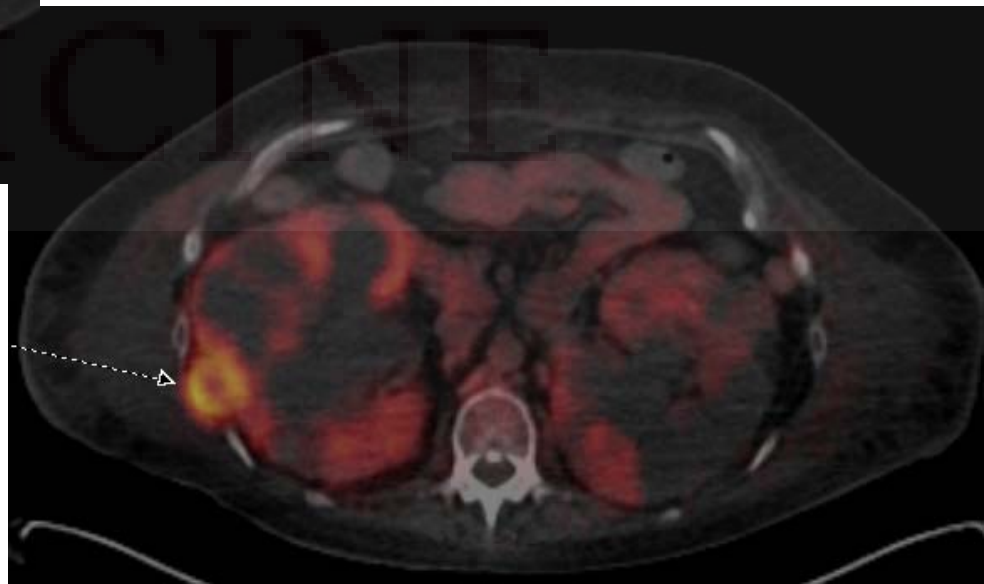
- 18-FDG PET scan:
  - 3 pts with histologically confirmed neuroendocrine tumors.
    - CT, MRI, octreotide scan failed to identify tumor or had changes of uncertain significance.
  - 2 pts with ectopic Cushings.
    - 1 patient with lung nodule on CT, confirmed on PET and histologically.
    - 1 patient with liver and bony mets on MRI, suspicious for primary uterine cancer on PET.
  - 5 patients with ectopic Cushings.
    - All had positive PET scans, 4 histologically confirmed.
    - All had negative CT abdomens (but all the cancers were in the thorax).

Kumar et al. Clin Endocrinol (Oxf). 2006 Apr;64(4):371-4.
Moares et al. Pituitary. 2009;12(4):380-3.
Xu et al. Endocrine. 2009 Dec;36(3):385-91.

PET scan





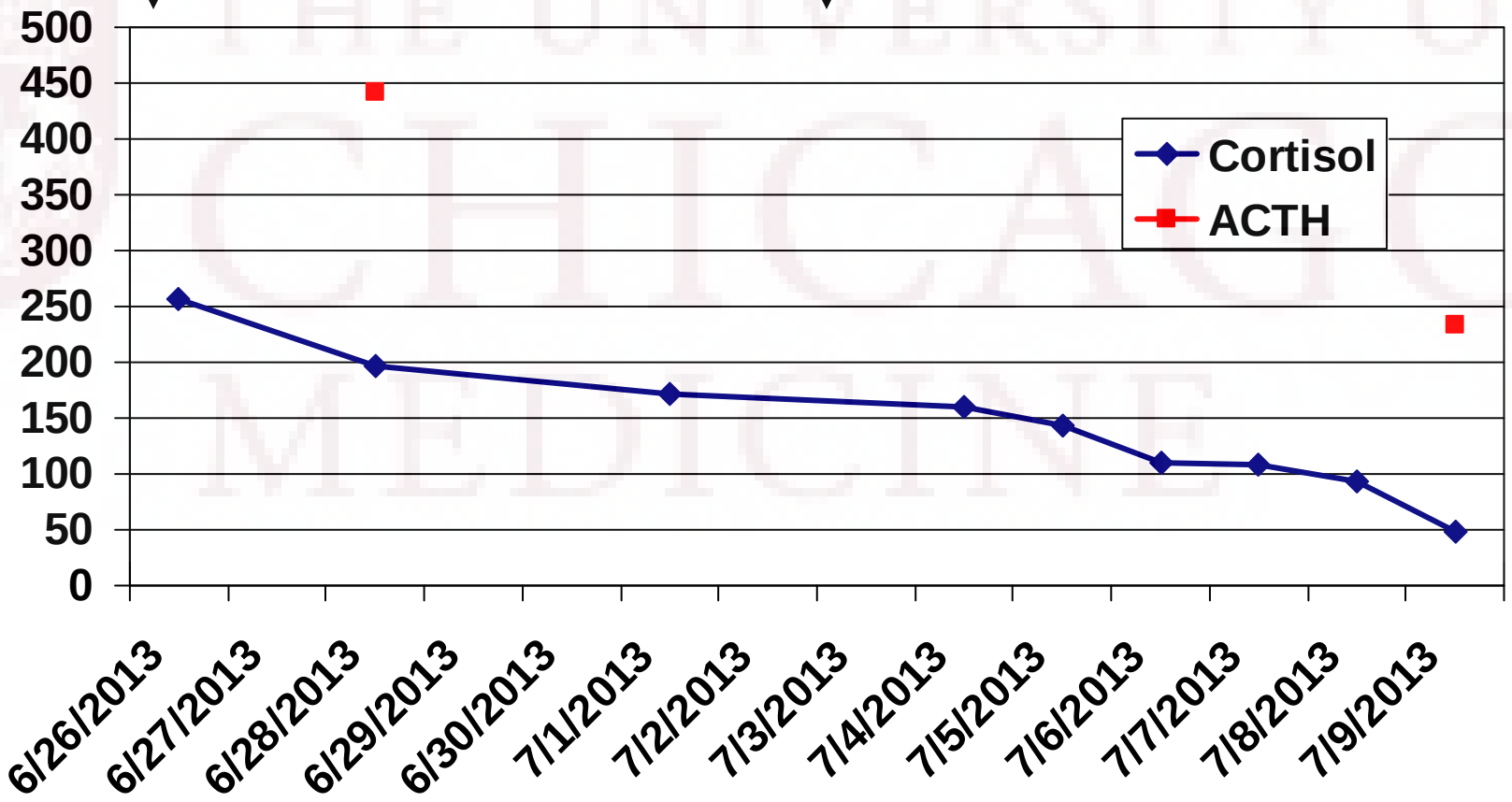


Clinical Course

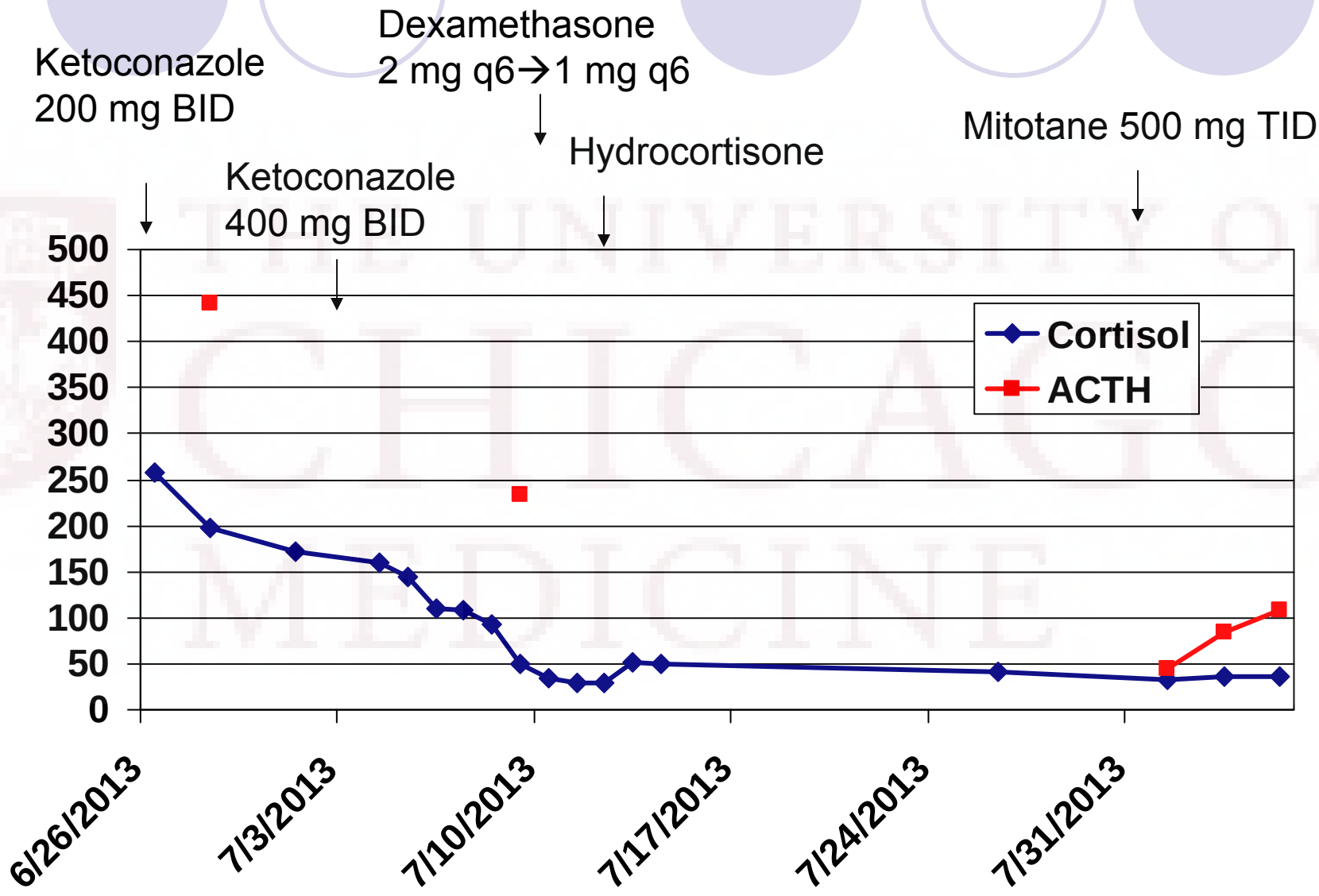
Ketoconazole 200 mg BID
(24 hr urine cortisol: 1183)

Ketoconazole 400 mg BID
(24 hr urine cortisol: 644)

24 hr urine cortisol: 285
(started HD)



Clinical Course



Quick review on meds for Cushings

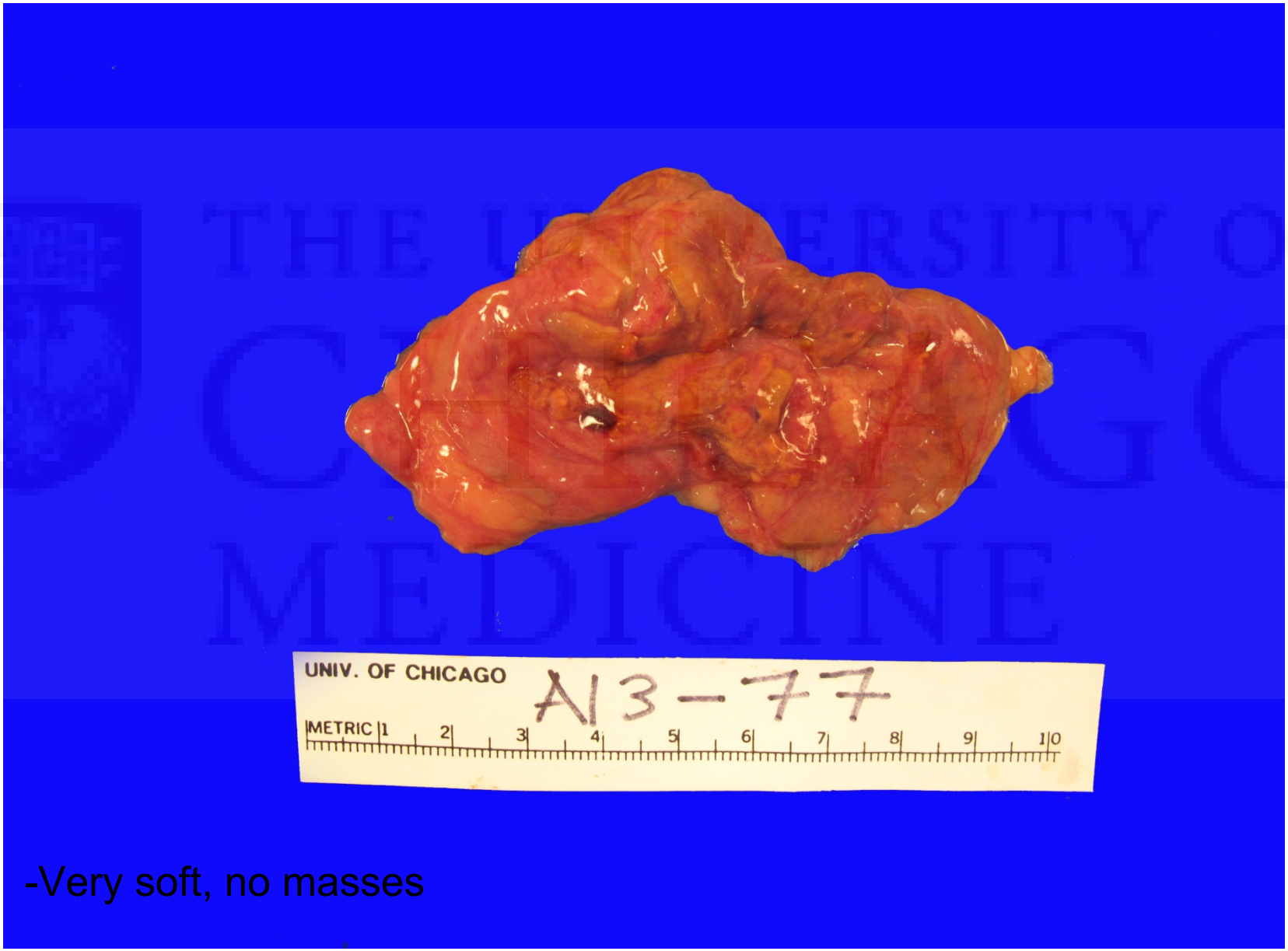
Drug	MOA	Efficacy/Benefits	AE/Limitations
Ketoconazole	Inhibits adrenal steroidogenesis	50% of patients with controlled cortisol.	Hepatotoxicity, hypogonadism, gynecomastia
Metyrapone	Inhibits adrenal steroidogenesis	Up to 80% of patients with controlled cortisol.	Escape, increased ACTH, hirsutism, hypokalemia, hypocortisolism
Mitotane	Inhibits adrenal steroidogenesis, “adrenolytic”	Up to 90% short-term remission in ectopic ACTH; up to 70% remission in Cushing’s disease.	Slow onset of action; poor tolerability due to neurologic, GI, and hepatic effects.
Mifepristone	Glucocorticoid receptor antagonist	Clinical responses in up to 87% of patients; improves glucose metabolism, insulin sensitivity, weight loss .	Hypokalemia, vaginal bleeding, inability to use cortisol levels for monitoring, nausea/ fatigue common.

Clinical Course

- CD4 count of < 8.
- Complicated by pneumonia with Pneumocystis, MRSA, CMV, and eventually aspergillus; C difficile; and Enterobacter and VRE septicemia.
- Both septic shock and ARDS were refractory to treatment and the patient was transitioned to comfort care.

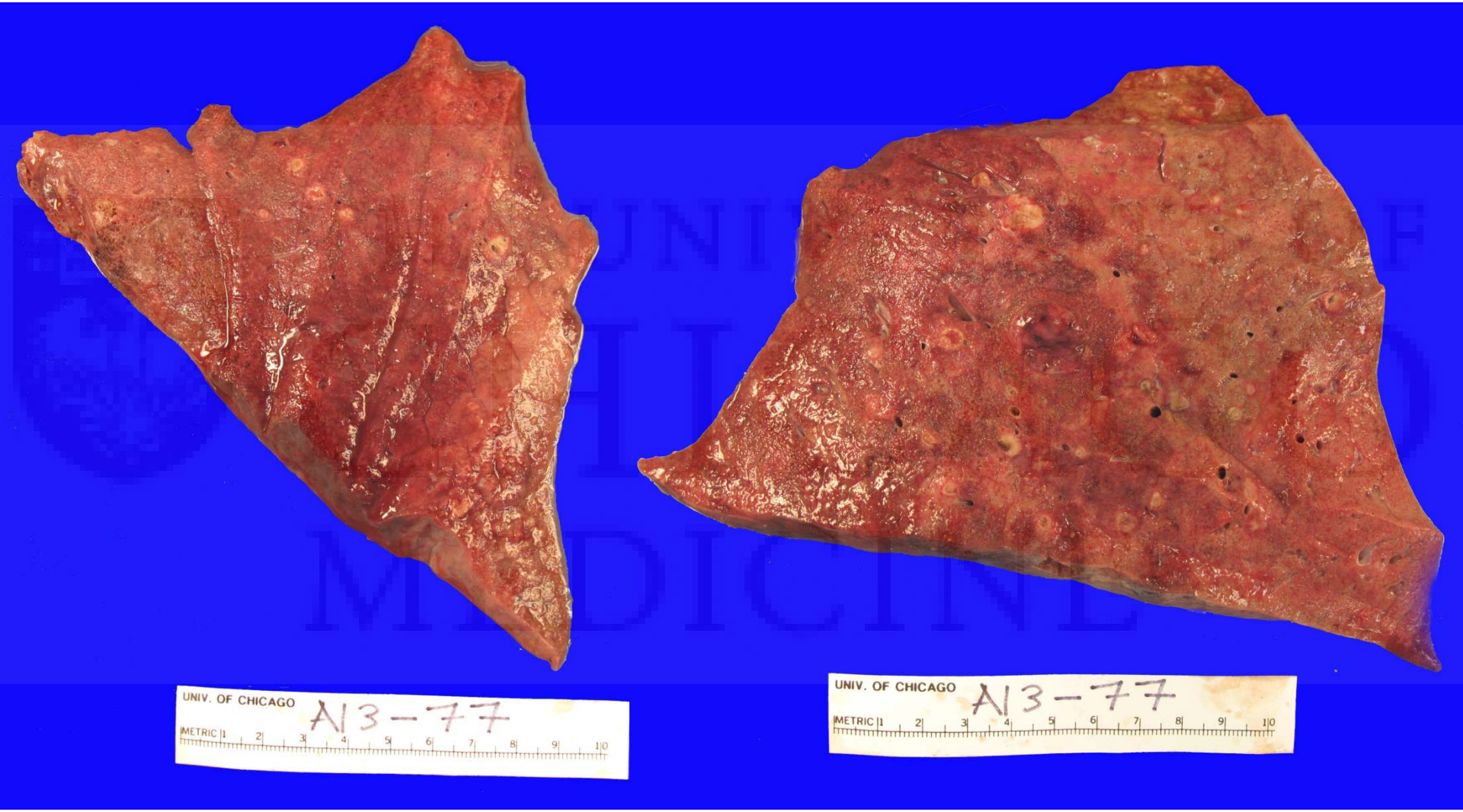
A13-77

Adrenals R-18.2g / L-19.6g (4-6g)



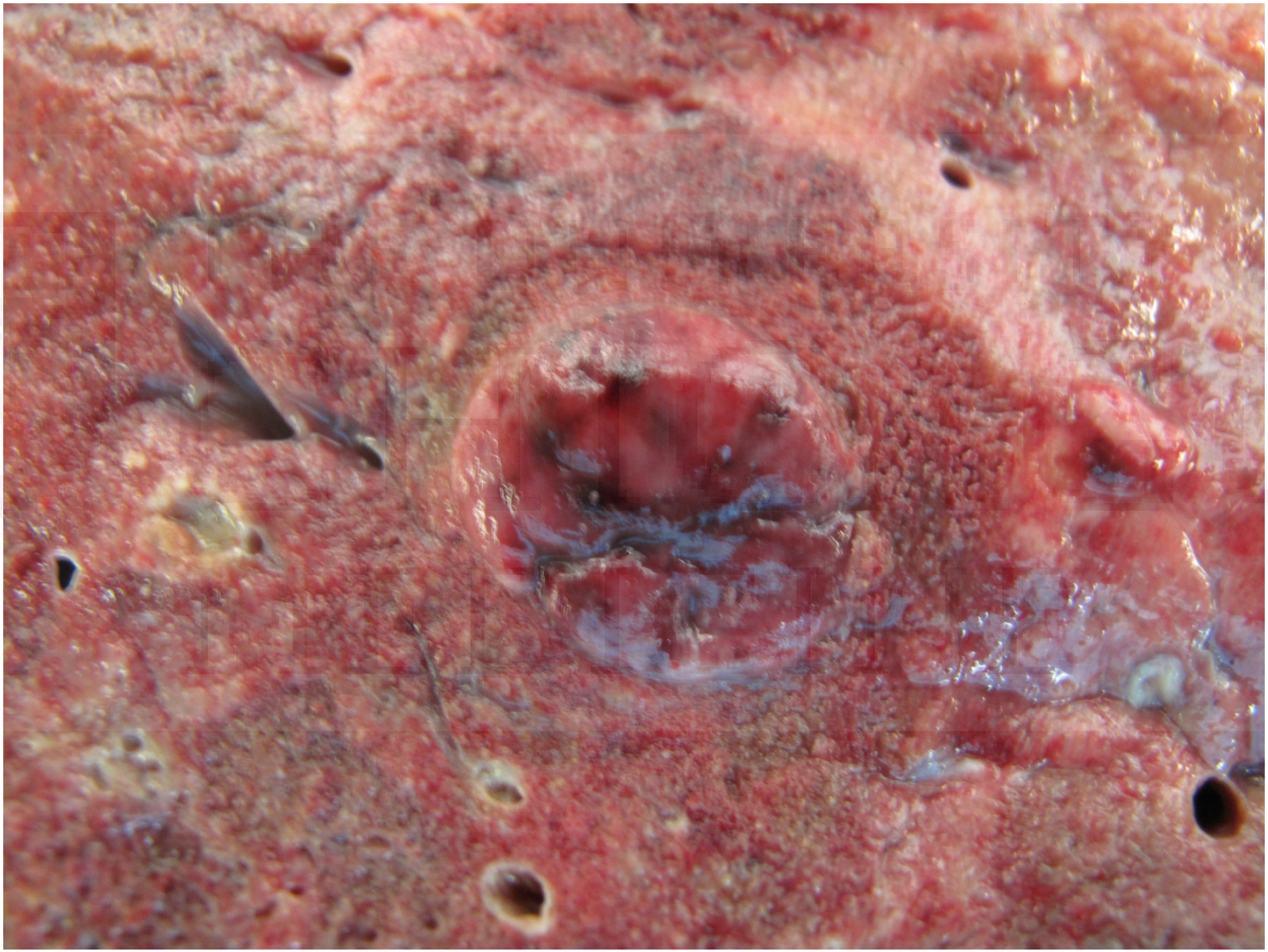
-Very soft, no masses

Lungs R-1265g /L-1104g (350-450g)



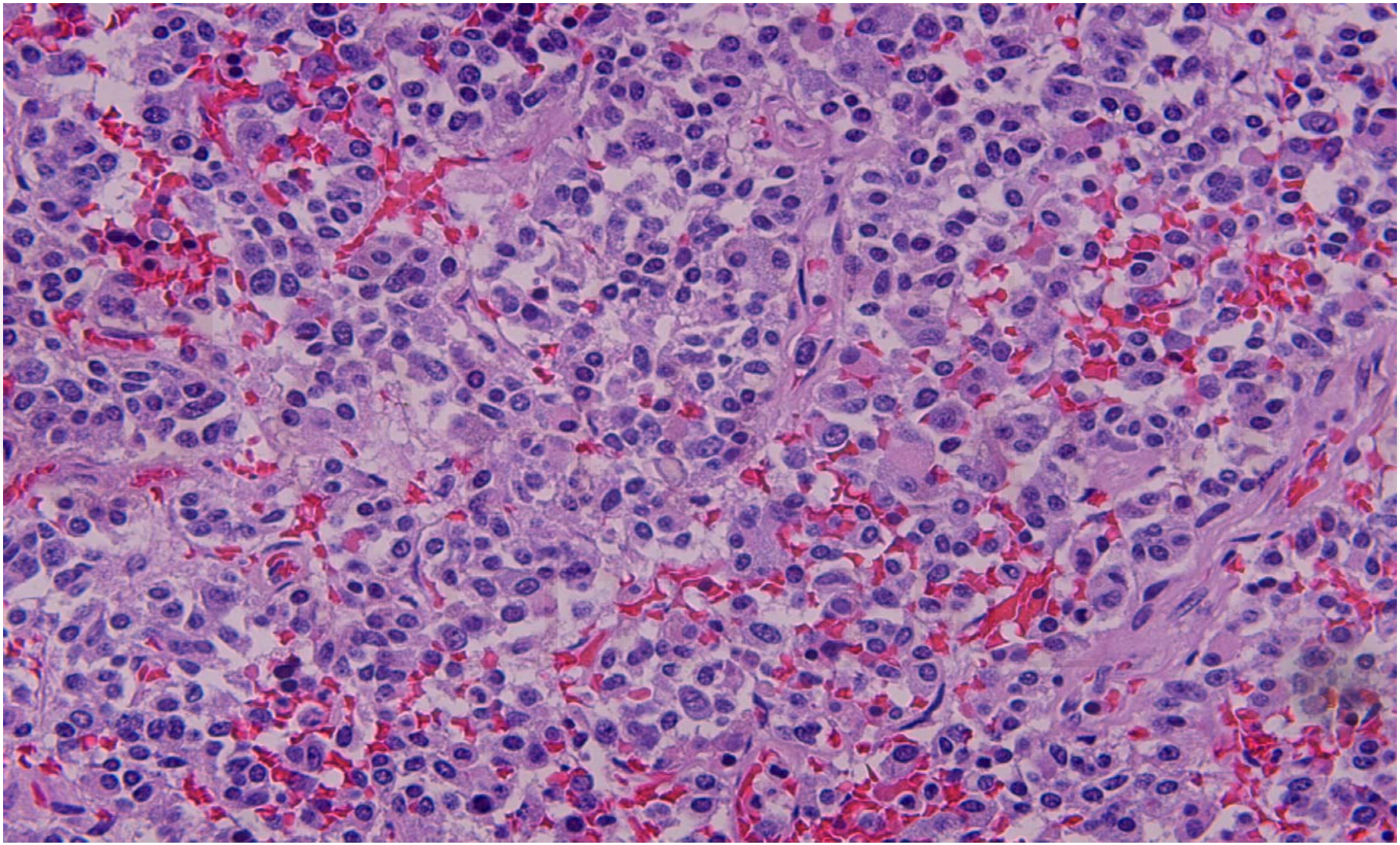
-firm, consolidated maroon parenchyma

Lungs R-1265g /L-1104g (350-450g)

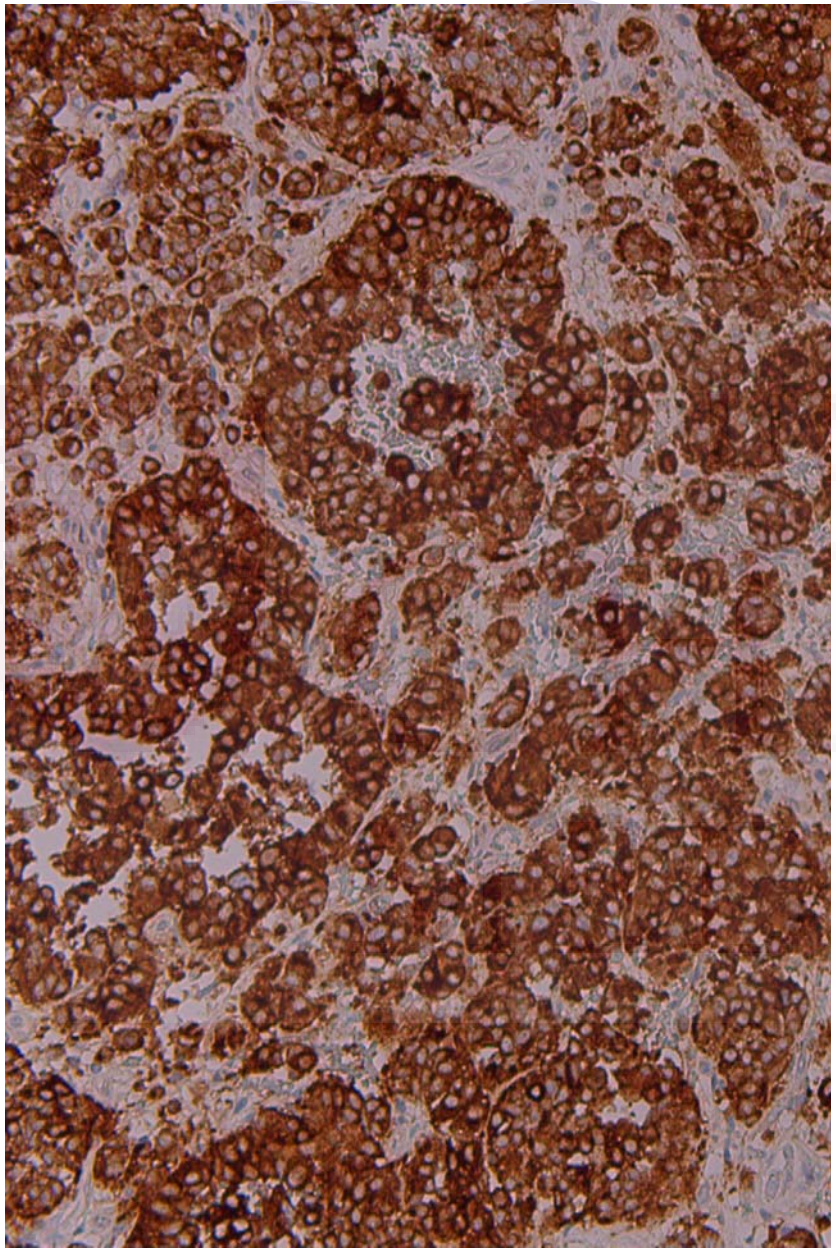


-well-circumscribed, bosselated, maroon nodule (1.8cm) in left lower lobe

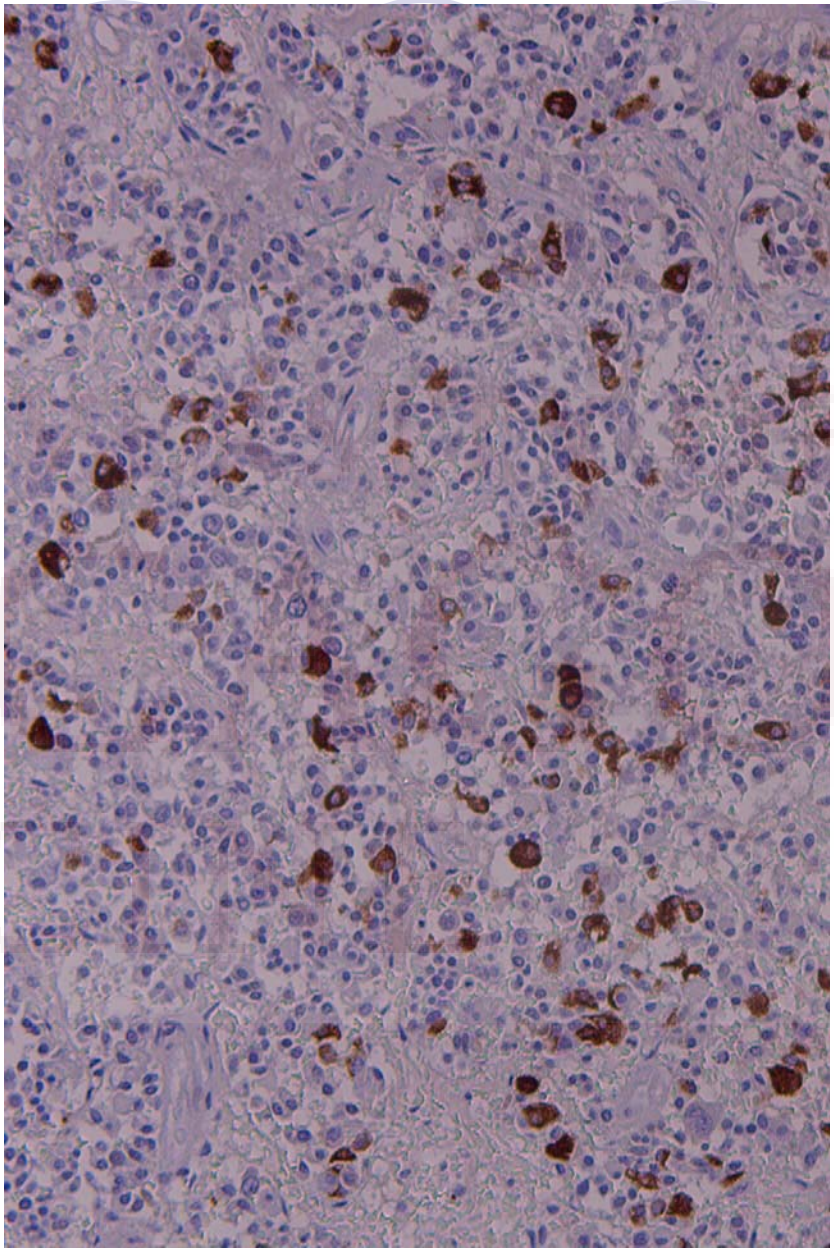
H&E



-Well-circumscribed mass of nested cells; very vascular
-Nuclei with coarse, “salt and pepper” chromatin, mitoses are extremely rare
-Carcinoid



Synaptophysin

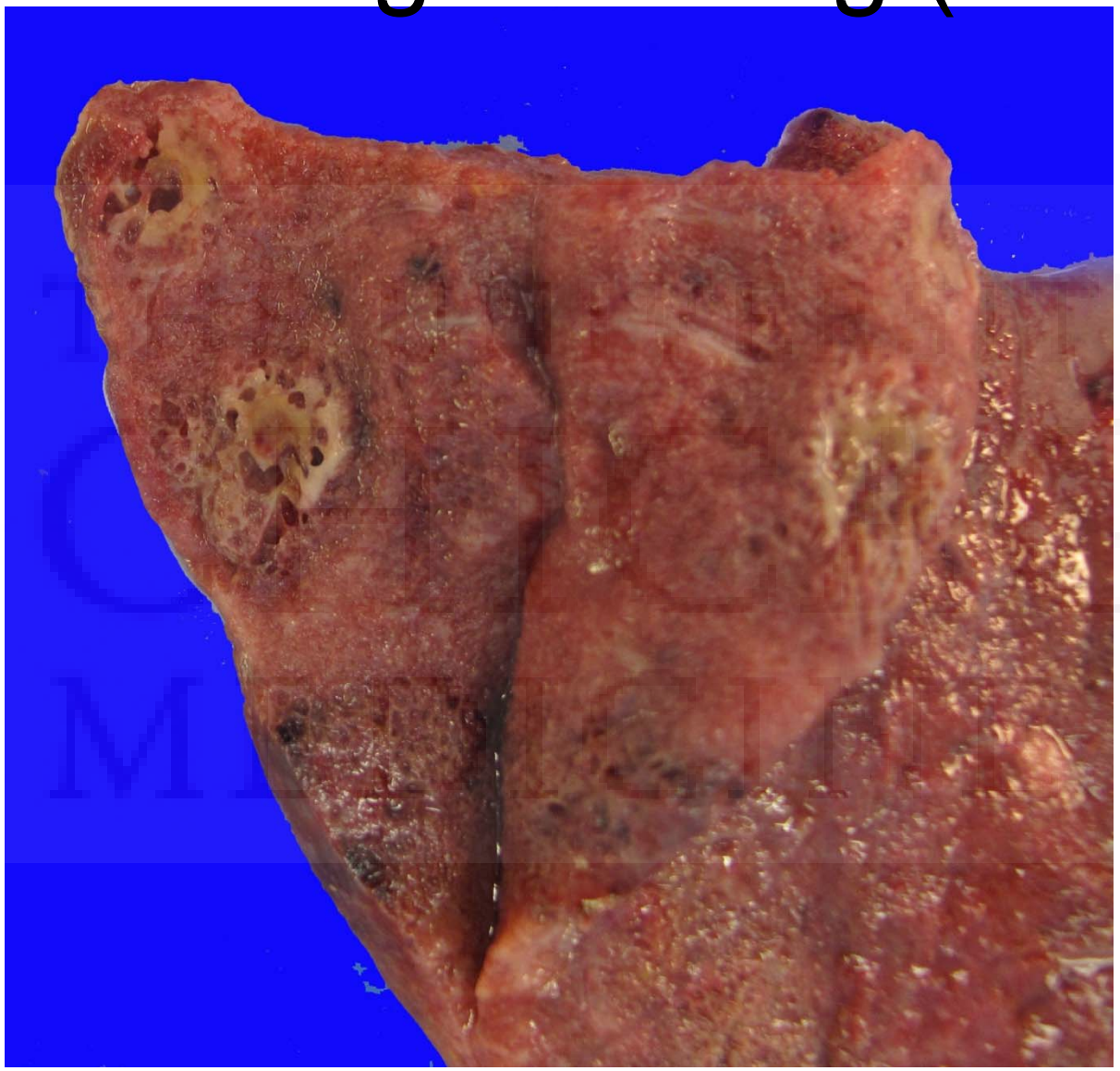


ACTH

Pituitary

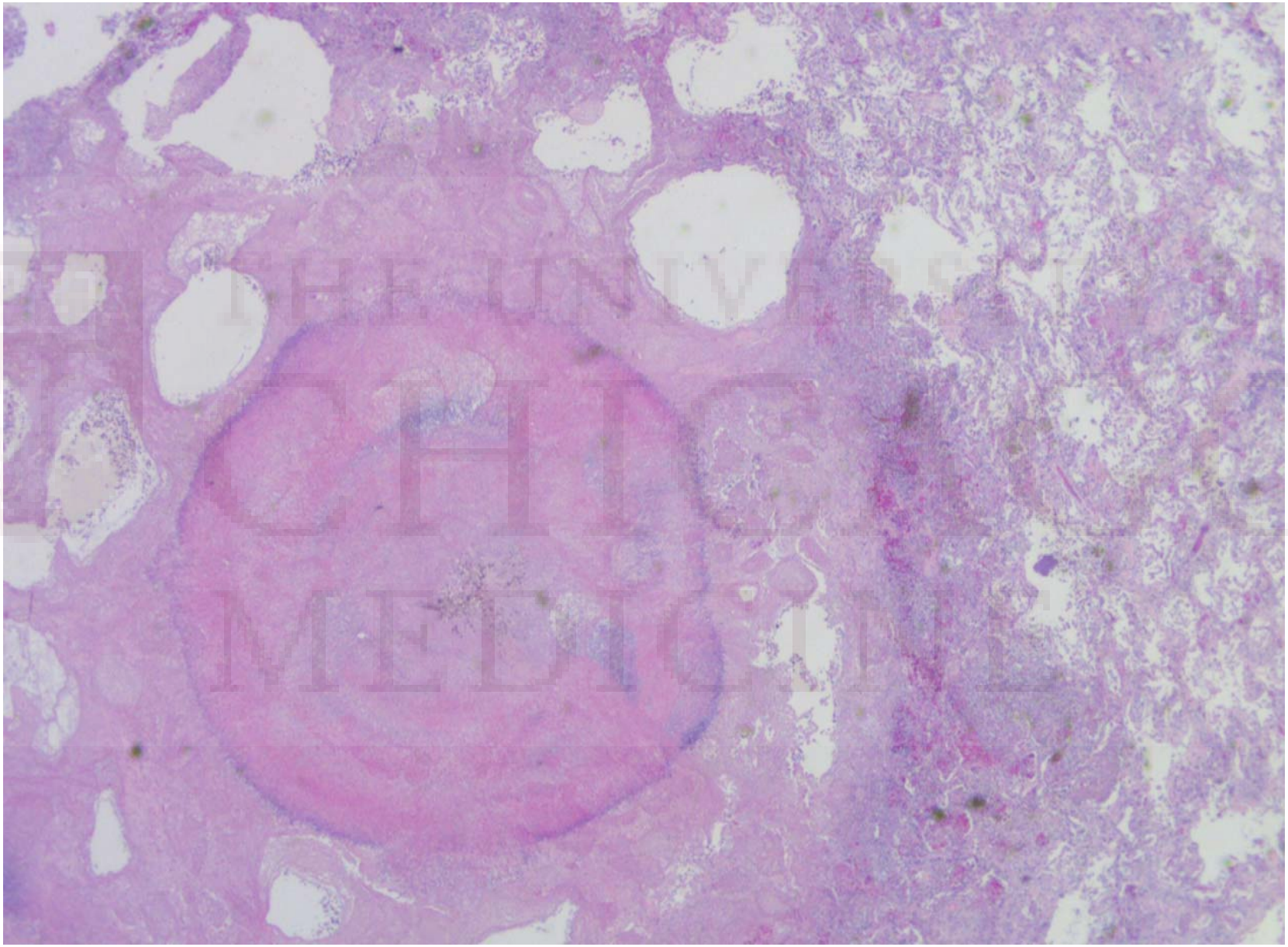
-Normal pituitary, no adenoma present

Lungs R-1265g /L-1104g (350-450g)



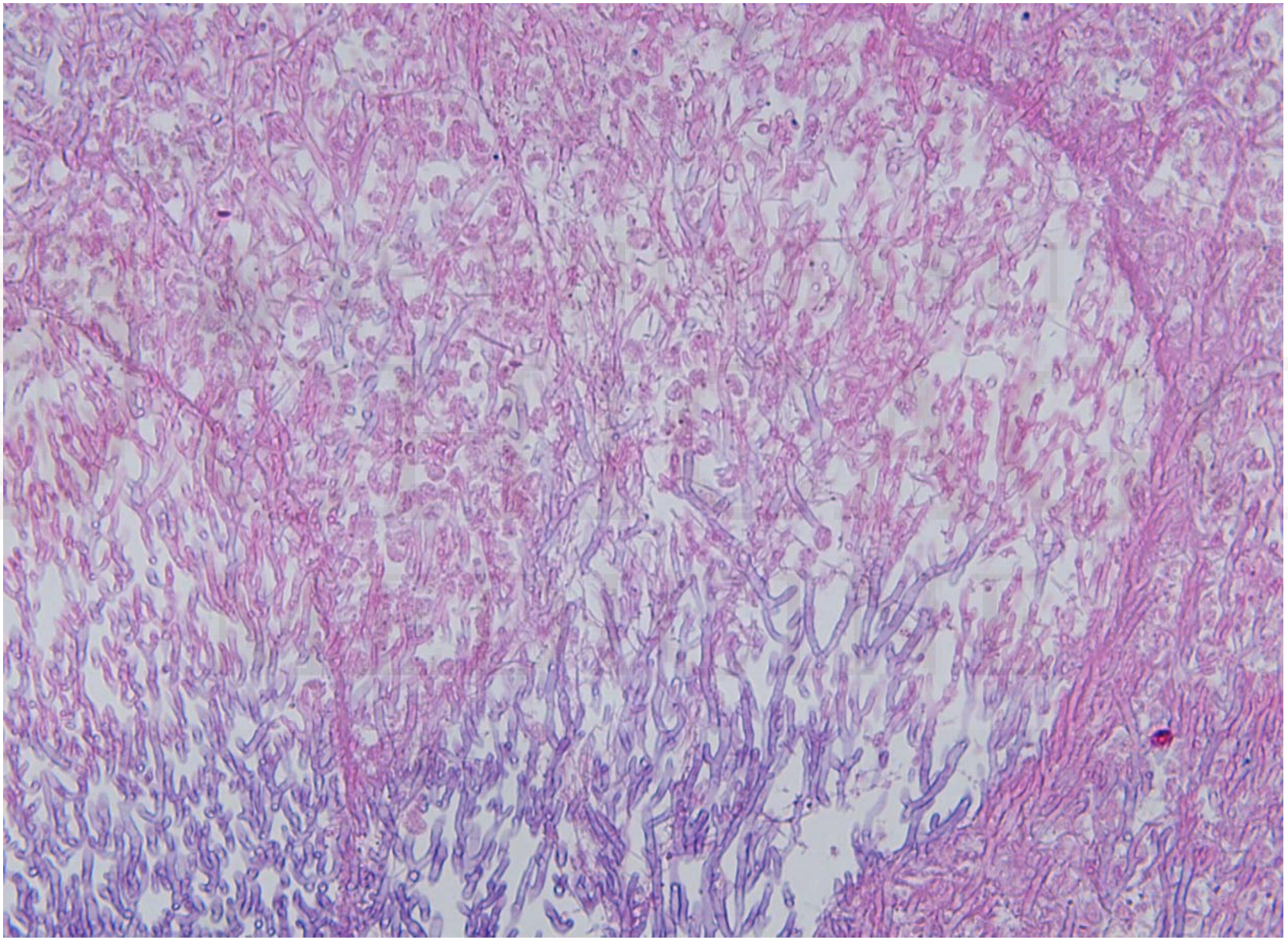
-multiple cavitary, hard, tan nodules ranging in size from 0.2-0.5 cm bilaterally

H&E

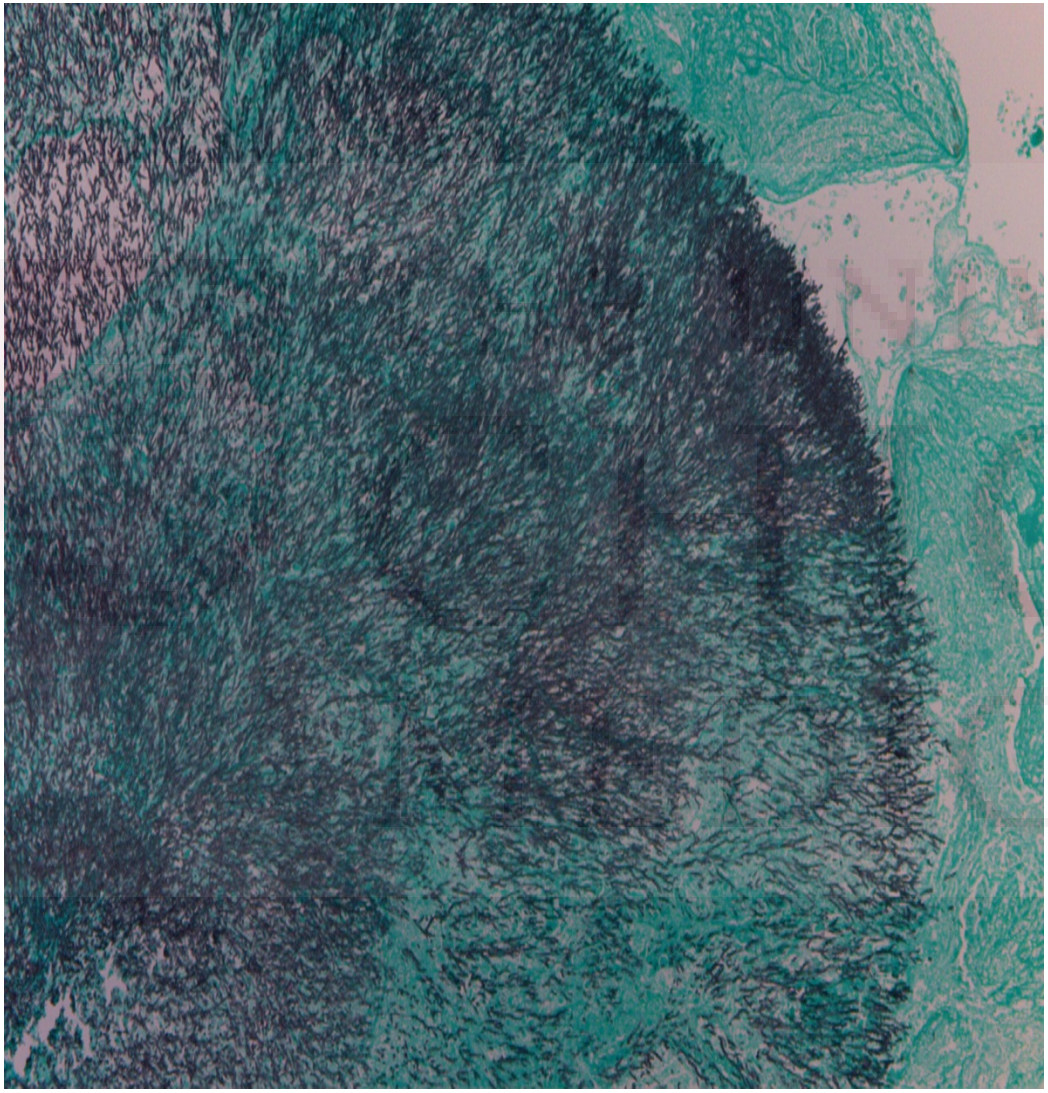


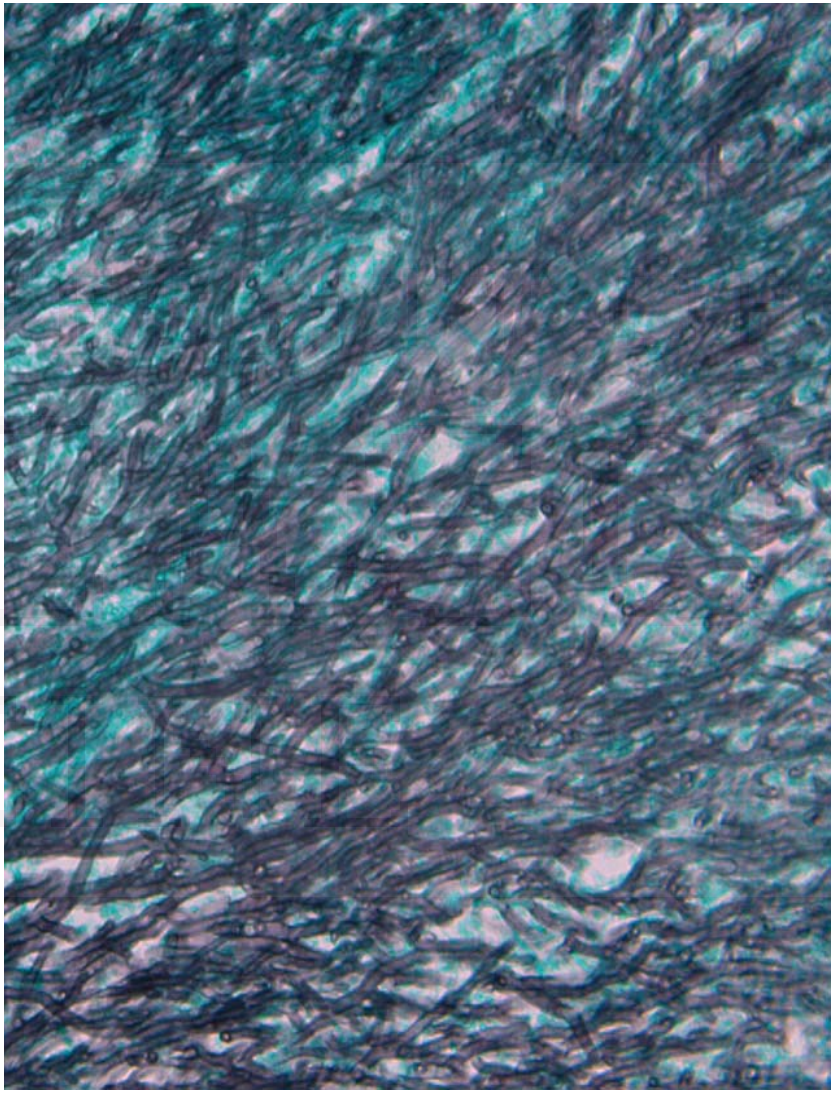
-What do we have here?

H&E



GMS Stain





-Yeast hyphae branching at acute angles – invasive aspergillus
-Post-mortem blood culture was positive for aspergillus

Lots of mysteries

- Thrombocytopenia?
- CD4 count?
  - 1 case report of a 50 year old man with declining CD4 counts in the setting of adrenocortical carcinoma and Cushings.
  - 1 study comparing lymphocyte percentages.

Table II. Percentages of specific lymphocyte subsets in Cushing's patients and matched normal controls*

Lymphocyte phenotype	Cushing's patients ($n = 20$)	Normal controls ($n = 20$)	p†
CD_3+	61.9 ± 22.7	66.8 ± 18.6	NS‡
CD_4+	35.4 ± 17.5	44.1 ± 12.4	< .05
CD_8+	27.1 ± 12.9	19.4 ± 8.2	< .05
CD_4/CD_8	1.67 ± 1.16	2.58 ± 1.13	< .01
CD_{56}+	15.0 ± 11.0	15.6 ± 7.2	NS

Lewis et al. J Am Board Fam Pract. 2000 May-Jun;13(3):219-21.
Kronfol et al. Psychoneuroendocrinology. 1996 Oct;21(7):599-608.

Cushings and PCP

- Incidence of opportunistic infections in Cushing's syndrome is 11-17%
  - Correlates with degree of hypercortisolemia
- Associated with glucocorticoid treatment
  - PCP prophylaxis is recommended in patients receiving ≥20 mg of prednisone daily for >1 mo and have an additional cause of immunocompromise.
- Case-reportable with Cushing's syndrome
  - The rapid reduction of cortisol levels may lead to PCP pneumonia.

Arlt et al. Exp Clin Endocrinol Diabetes. 2008 Oct;116(9):515-9.
Sarlis et al. J Clin Endocrinol Metab. 2000 Jan;85(1):42-7.

Ectopic Cushing's and PCP

Case (Ref.)	Sex/Age (years)	medical treatment	Onset of symtoms of PCP after initiation of therapy	Symptoms & signs of PCP	Mechanical ventilation	Clinical outcome
1 (Oosterhuis et al., 2007)	F/62	mifepristone spironolactone	few days	dyspnoea; CXR: bilateral infiltrates	no	survived
2 (Oosterhuis et al., 2007)	F/57	ketoconazol mifepristone spironolactone	2	dyspnoea; tachypnoea; CXR: bilateral alveolo-intestinal opacities	yes	survived
3 (Keenan et al., 2006)	F/26	ketoconazol metyrapone	14	fever, cough, shortness of breath; CXR: bilateral perihilar infiltrates	no	survived
4 (Fulkerson and Newman, 1984)	F/38	metyrapone	1	productive cough, dyspnoea; CXR: right lower upper lobe infiltrates	yes	died
5 (Kim et al., 2000)	F/60	ketoconazol octreotid	3	no specific chest symptoms after 3 days; after 4 days severe hypoxia; CXR: bilateral patchy infiltrative lesions	yes	died
present case (Arlt et al.)	M/36	metyrapone hydrocortison	14	fever, cough, shortness of breath; CXR: bilateral diffuse infiltrates and small pneumothoraces	yes	died
7 (Gabalec et al. 2011)	F/60	ketoconazole/etomidate	4	respiratory distress	no	survived
8	M/20	ketoconazole/etomidate	4	fever	no	survived
9 present case	**F/33**	**ketoconazole/mitotane**	**6**	**respiratory distress**	**yes**	**died**

Arlt et al. Exp Clin Endocrinol Diabetes. 2008 Oct;116(9):515-9.

Cushing's and PCP

- Severe PCP is characterized by neutrophilic lung inflammation, resulting in phagocytosis and release of proinflammatory cytokines.
- The degree of lung inflammation is more closely correlated with respiratory impairment and mortality than is the burden of p. jirovecii.
- Reducing cortisol levels (and allowing the immune system to activate) may be a promoting factor for onset of pneumonia in asymptomatic carriers.

Arlt et al. Exp Clin Endocrinol Diabetes. 2008 Oct;116(9):515-9.

The Answer

- Which of the following medications would you recommend to treat her hypercortisolism and prevent short-term comorbidity?
  - Octreotide and cabergoline
  - Etomidate and trimethoprim-sulfamethoxazole
  - Mitotane and alendronate
  - Ketoconazole and prednisone
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Take Home Message

- Don’t delay definite treatment as they can get sicker quickly.
- Start PCP prophylaxis in patients with severe hypercortisolemia before you start treating them.

References

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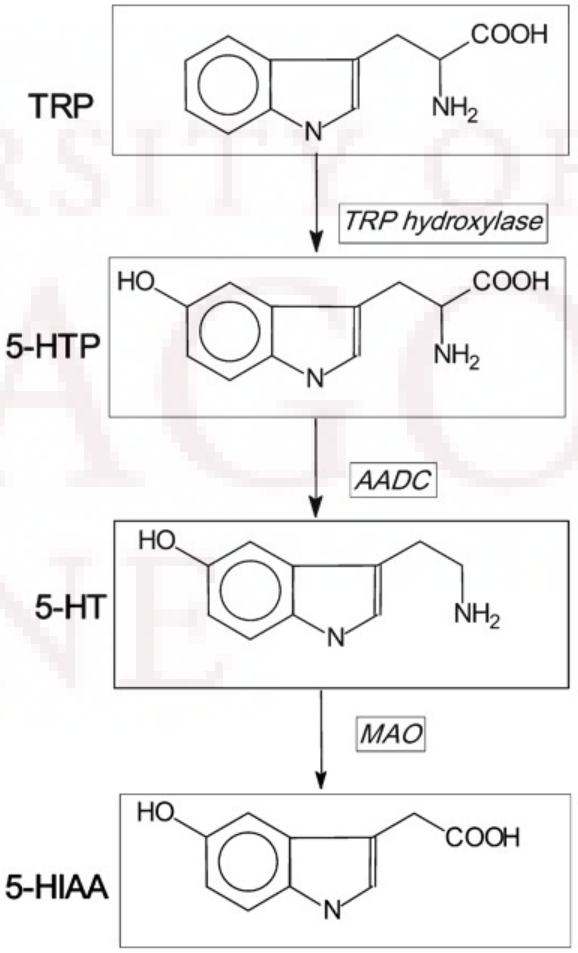
- Xu et al. Endocrine. 2009 Dec;36(3):385-91.

Imaging Modalities

- 11C-5-hydroxytryptophan PET:
  - 9 patients w/neuroendocrine tumors but neg. CT, MRI, and octreotide scan.
    - Detected primary tumor lesion in 3 patients, residual disease in 3 patients, and restaged 1 patient with MTC and hepatic mets.
- Patient had a 5-hydroxyindoleacetic acid of 2.1 (nl <8).



Nikolaous et al. J Endocrinol Invest. 2010 Dec;33(11):794-9.

Octreotide challenge

	Baseline	2 hrs	4 hrs	6hrs	8 hrs
ACTH	233	221	270	216	209
Cortisol	49.4	38.5	39.4	34.7	35.5

- Inhibits ACTH secretion
- Poorly effective for Cushing's disease but 50% response in ectopic ACTH
- Short-term response