John Sutton, DO, FACOI, FACE, CCD

Carson Tahoe Endocrinology

Carson City, NV

KCOM Class of 1989

Gonadal Physiology and Disease

No Disclosures

Gonadal Axis

- Hypothalamic-pituitary-gonadal
- Feedback mechanisms important
- Without production of hormone end products, axis should respond

Hypergonadotropic Hypogonadism

- Elevated gonadotropins (LH/FSH)
- Low gonadal hormones

Hypogonadotropic Hypogonadism

- Low or inappropriately normal gonadotropins
- Low gonadal hormones

24 Year Old Male

- Female body habitus
- Lack of secondary sex characteristics
- Absent facial hair
- Infertility
- Physical exam: small testicles, Tanner I

Laboratory

- Elevated LH, FSH, Low testosterone total, free and bioavailable
- Normal prolactin
- Normal thyroid function
- Pituitary is responding appropriately to an end organ hormonal deficiency

Diagnosis

Hyper-gonadotropic Hypogonadism

Additional Testing

- Karyotype: check for Klinefelter syndrome 47 XXY

Hypergonadotropic Hypogonadism

- Germ cell arrest
- Surgery, chemotherapy
- Mumps
- Alcohol
- Immune
- Intra-abdominal testicles

14 Year Old Male

- Lack of secondary sex characterisitics
- Gynecomastia

Laboratory

- Low LH, FSH
- Low total and low bioavailable (active) testosterone
- Normal prolactin
- Normal thyroid function

Diagnosis

Hypo-gonadotropic Hypogonadism

Differential Diagnosis

- Delayed puberty
- Kallman syndrome: anosmia, deficiency in GnRH
- Hyperprolactinemia
- Hemochromatosis or infiltrative
- Hypopituitarism
- Neoplasm (Brain or pituitary)
- Anorexia, excess exercise

Treatment

- If fertility is in question, will require HCG or GnRH administration
- For restoring male hormone levels without fertility: testosterone IM, transdermal patch or gel, including axillary administration
- Exogenous Testosterone suppress axis may affect future fertility

Hyperprolactinemia

- Hypothyroidism
- Pituitary neoplasm
- Non-fasting
- Medications

- TREATMENT: Medical

44 Year Old Male

- Breast tenderness, decreased sex drive
- Breast enlargement, normal genital exam

Laboratory

- Normal estradiol, low free and total testosterone
- Normal B-HCG
- Normal gonadotropins
- High prolactin
- Normal thyroid function

Diagnosis

Hypogonadotropic Hypogonadism due to Hyperprolactinemia

Treatment

- Evaluate MRI for pituitary/brain lesion
- Treatment of pituitary lesion: medical with Cabergoline or Bromocriptine as Dopamine Agonist
- Rarely require pituitary surgery
- Visual field testing if large tumor & compressing optic chiasm

Differential Diagnosis

- Gynecomastia common in elderly, obese, puberty
- High estradiol may represent a testicular or adrenal neoplasm
- High HCG suggests testicular or pulmonary neoplasm
- Hypothyroidism

Differential Diagnosis

- **Hypothyroidism**: promotes increased prolactin, suppression of gonadotropins, low male hormone, infertility, gynecomastia

16 Year Old Female

- Lack of secondary sex characteristics
- No menses, primary amenorrhea

Laboratory

- Low LH, FSH
- Low estradiol

Diagnosis

Hypo-gonadotropic Hypogonadism

Hypogonadotropic Hypogonadism

- Pituitary tumors
- Kallman syndrome (anosmia)
- Anorexia Nervosa
- Excessive exercise

Additional Findings with similar history but elevated LH & FSH

- Short stature
- Prepubertal genital exam
- These patients have primary amenorrhea with no history of menses
- Secondary amenorrhea refers to absent menses after menarche

Diagnosis

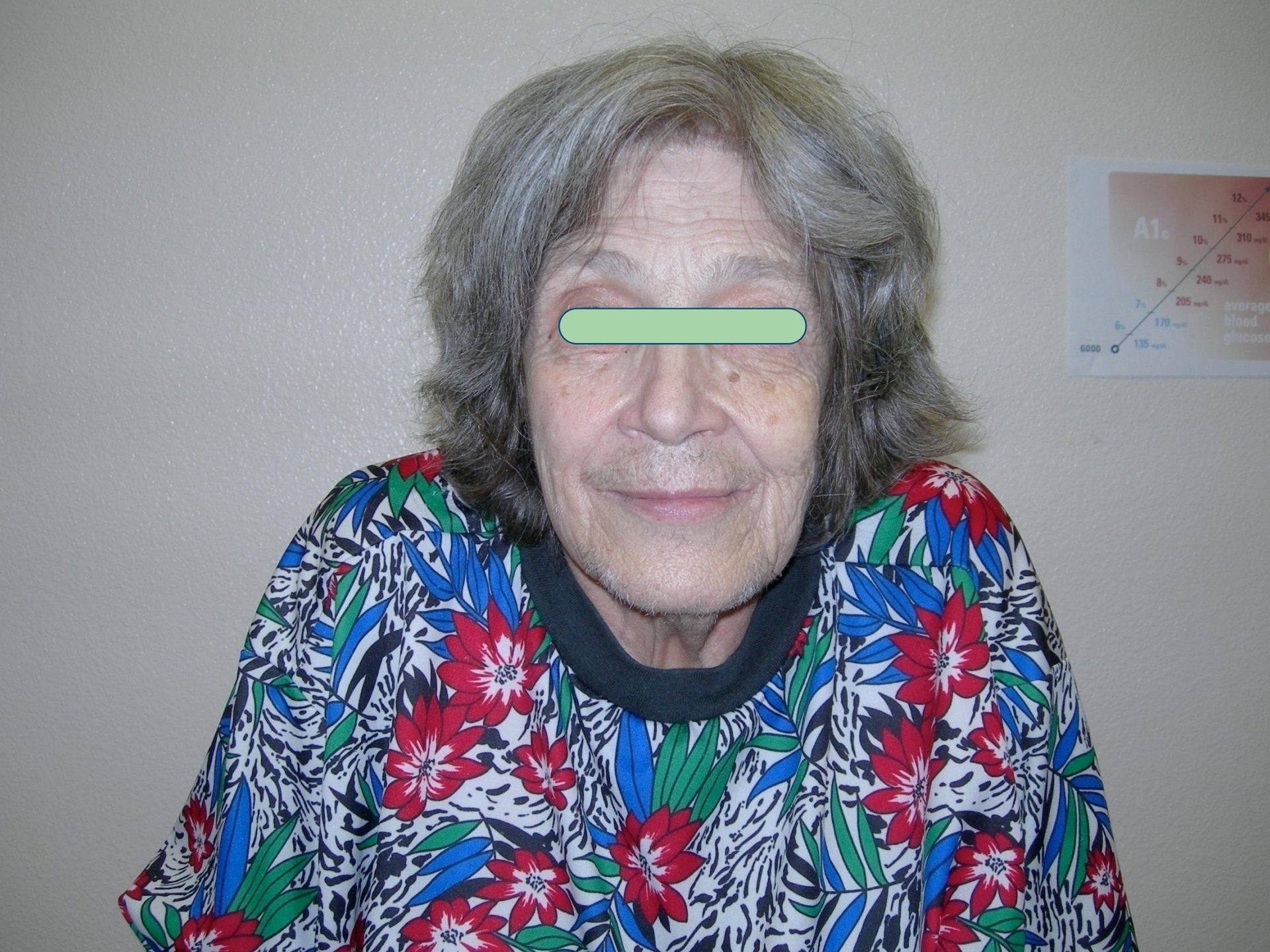
Hypergonadotropic Hypogonadism
Turner Syndrome

Hypergonadotropic Hypogonadism

- Menopause ovarian failure
- Surgical removal of ovaries
- Turner Syndrome 45 X0

Secondary Amenorrhea

- Polycystic ovarian syndrome: adequate estrogen, excess androgen
- Uterine defects and trauma
- Pregnancy, profound stress
- Systemic illness


A1c
12%
11%
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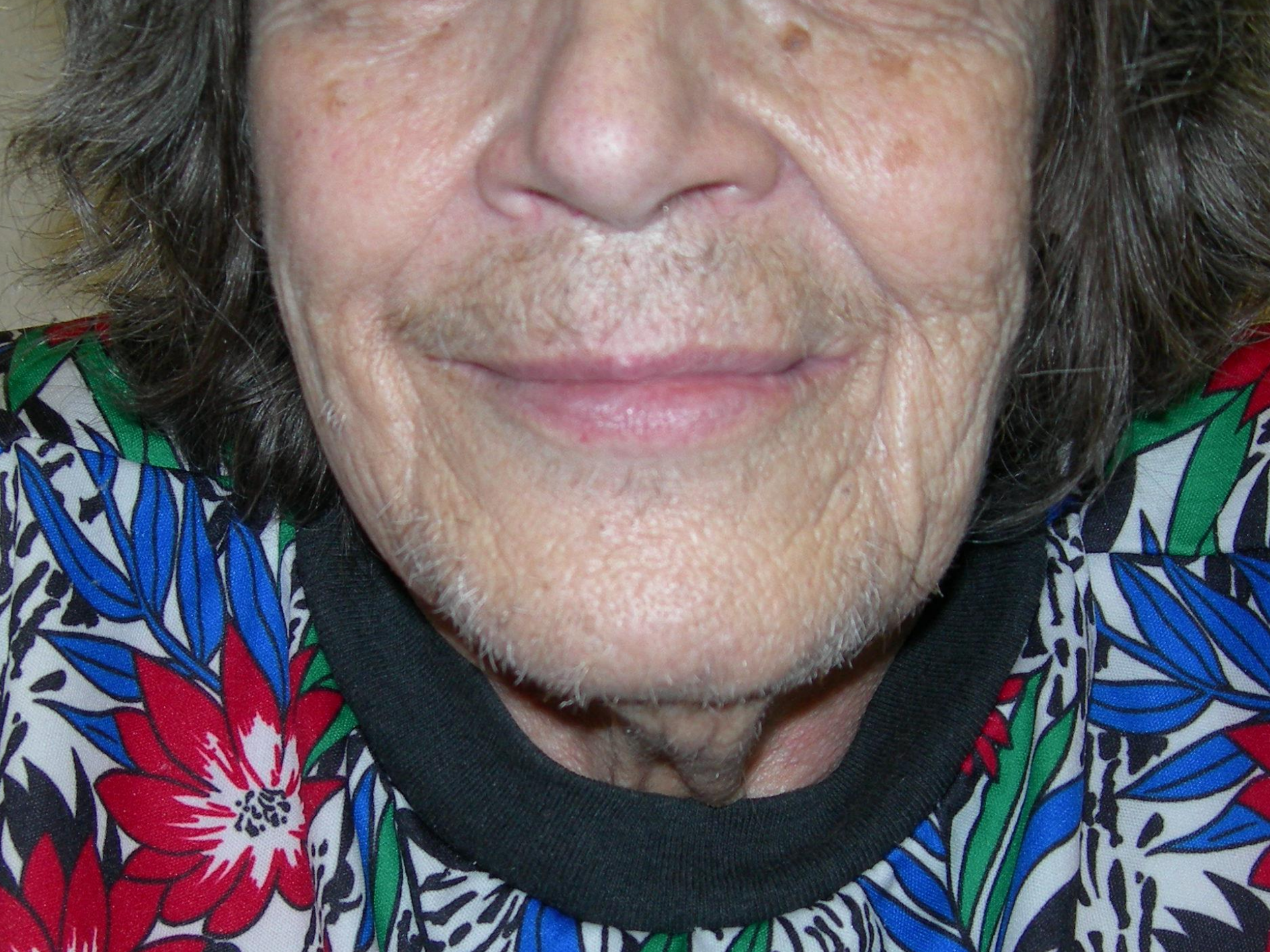
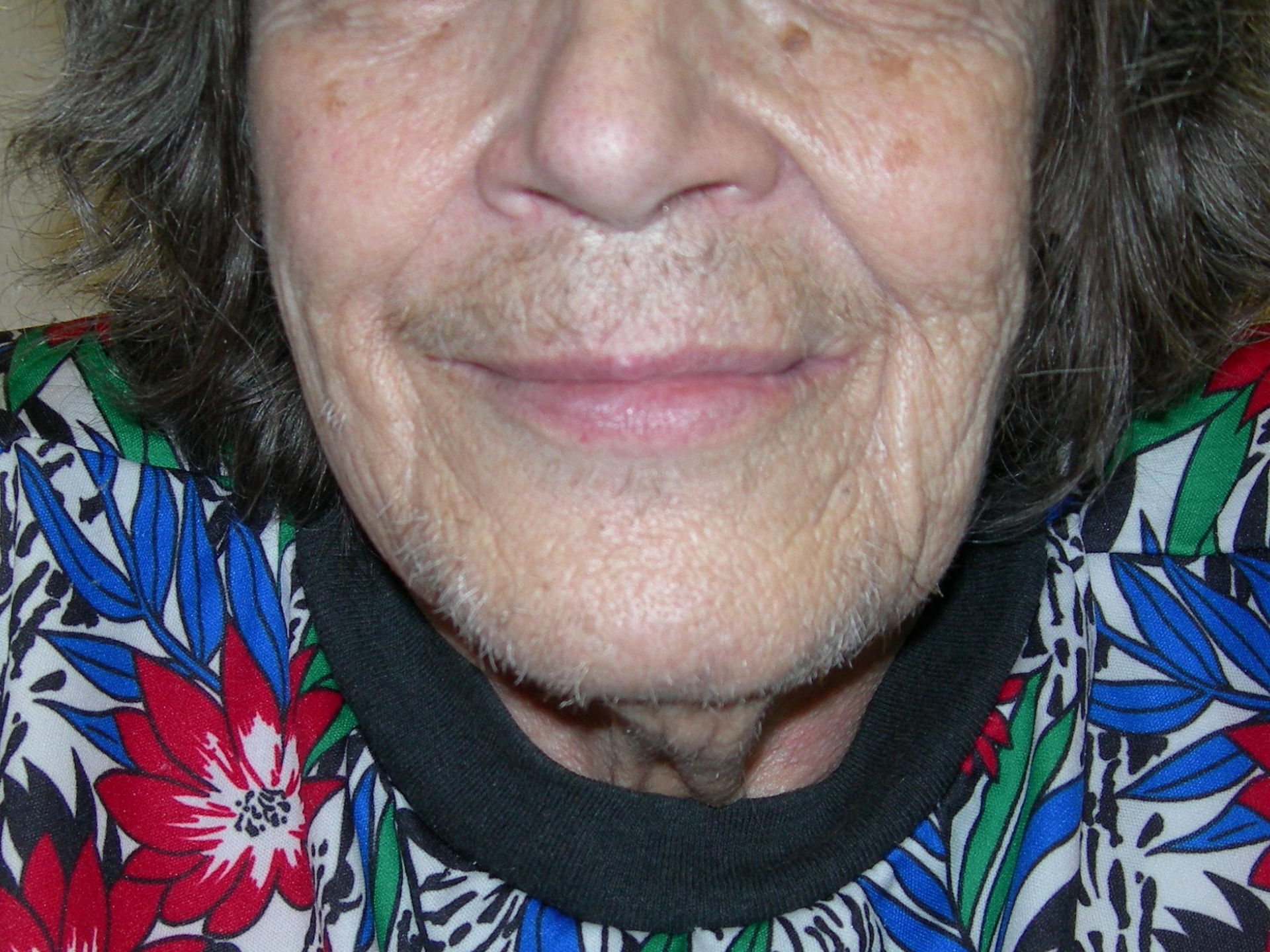


Hirsutism

- Check DHEAS and Total testosterone: Neoplasm considered with DHEAS twice normal(adrenal) and Testosterone total > 200 ng/dl (ovarian) or as low as 150 ng/dl

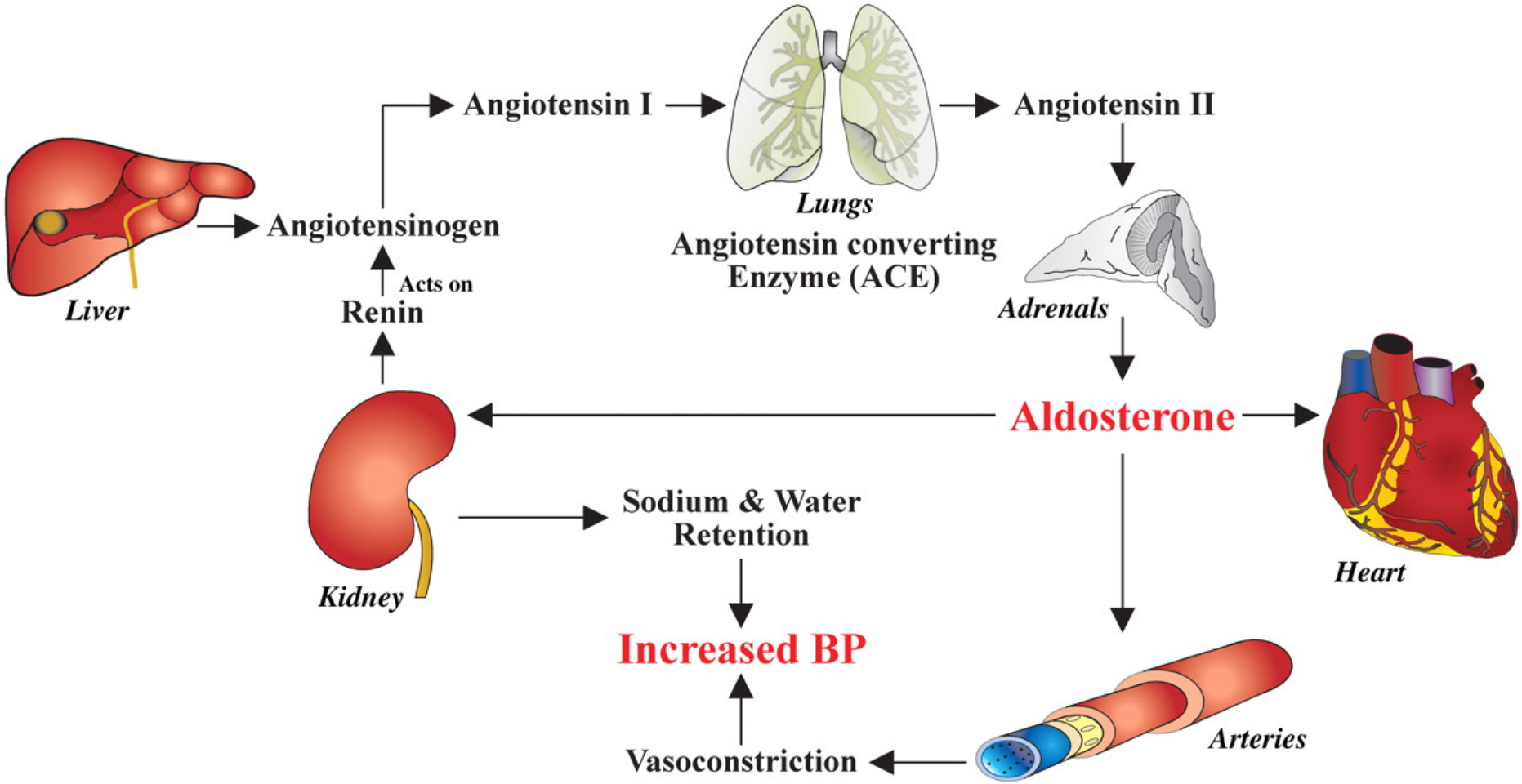
- Consider congenital adrenal hyperplasia, Cushing Syndrome, virilizing tumors, PCO



Disease of the Adrenals

Zona Glomerulosa

- Mineralocorticoids: aldosterone
- Angiotensin II/renin regulation by sympathetic tone; High potassium will stimulate and ACTH
- Increase in aldosterone leads to salt and water retention
- Increase in Angiotensin II leads to vasoconstriction

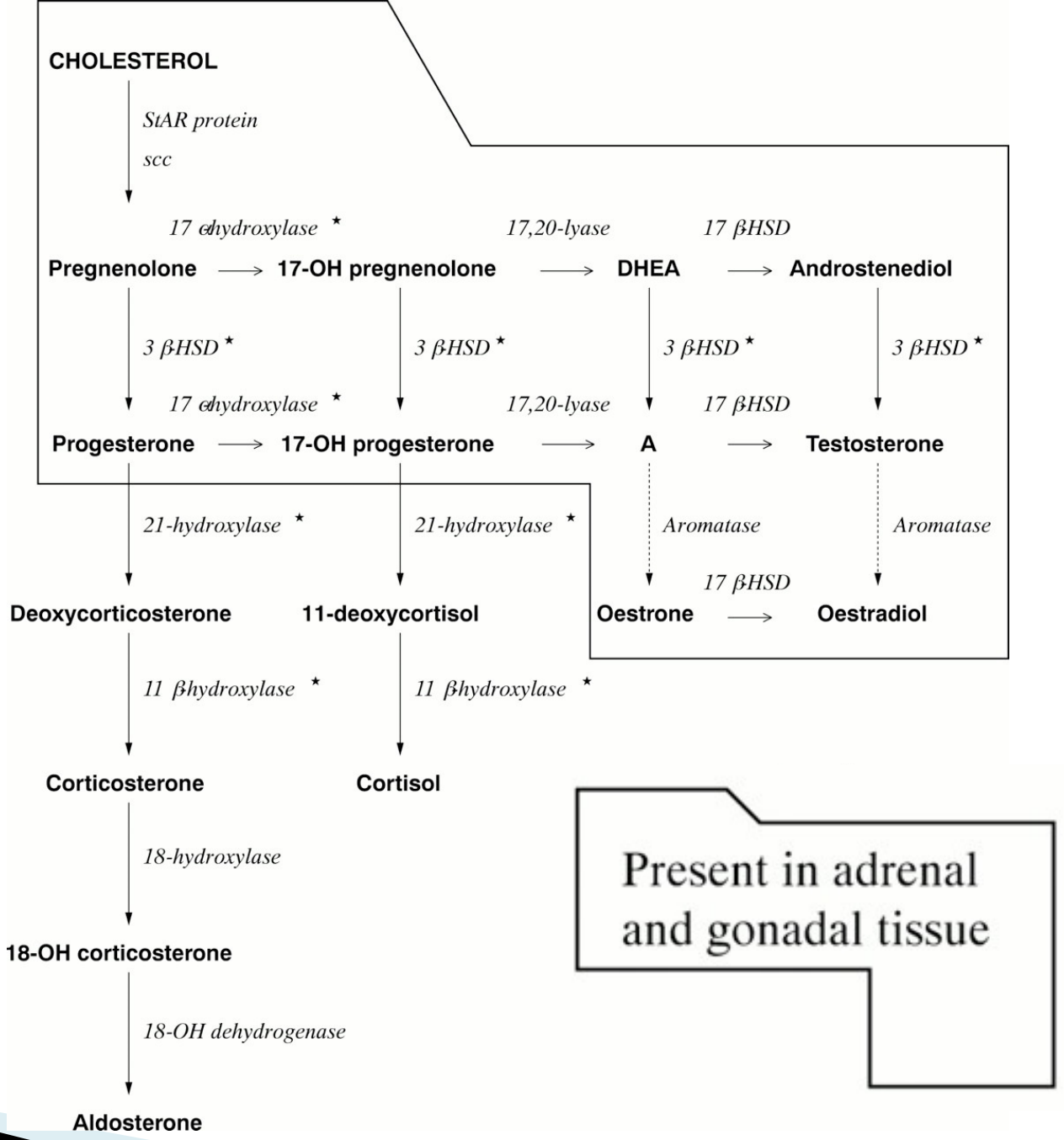

Angiotensin I
Angiotensin II
Lungs
Angiotensin converting
Enzyme (ACE)
Liver
Angiotensinogen
Acts on
Renin
Adrenals
Aldosterone
Heart
Kidney
Sodium & Water
Retention
Increased BP
Arteries
Vasoconstriction

Zona Fasiculata and Reticularis

- Glucocorticoids: Cortisol
- Androgen: DHEAS
- Regulated by ACTH

Steroid Production Pathway (steroidogenesis)

- Baseline substrate = cholesterol
- Precursors: DHEAS
  17-OH progesterone
- End products: estradiol, cortisol, aldosterone


CHOLESTEROL
StAR protein
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17,20-lyase
17 βHSD
Pregnenolone
17-OH pregnenolone
DHEA
Androstenediol
3 βHSD ★
3 βHSD ★
3 βHSD ★
3 βHSD ★
17 αhydroxylase ★
17,20-lyase
17 βHSD
Progesterone
17-OH progesterone
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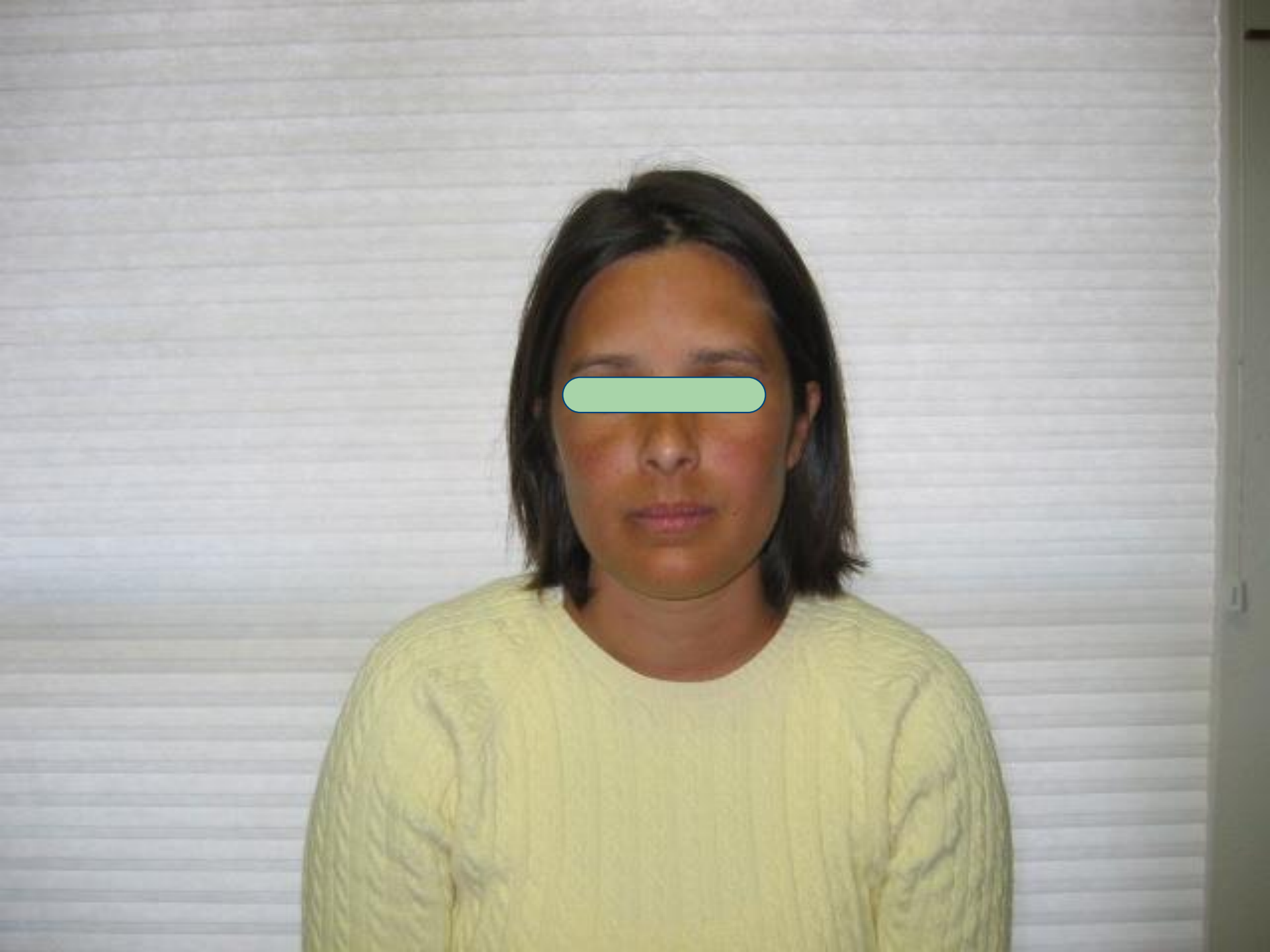
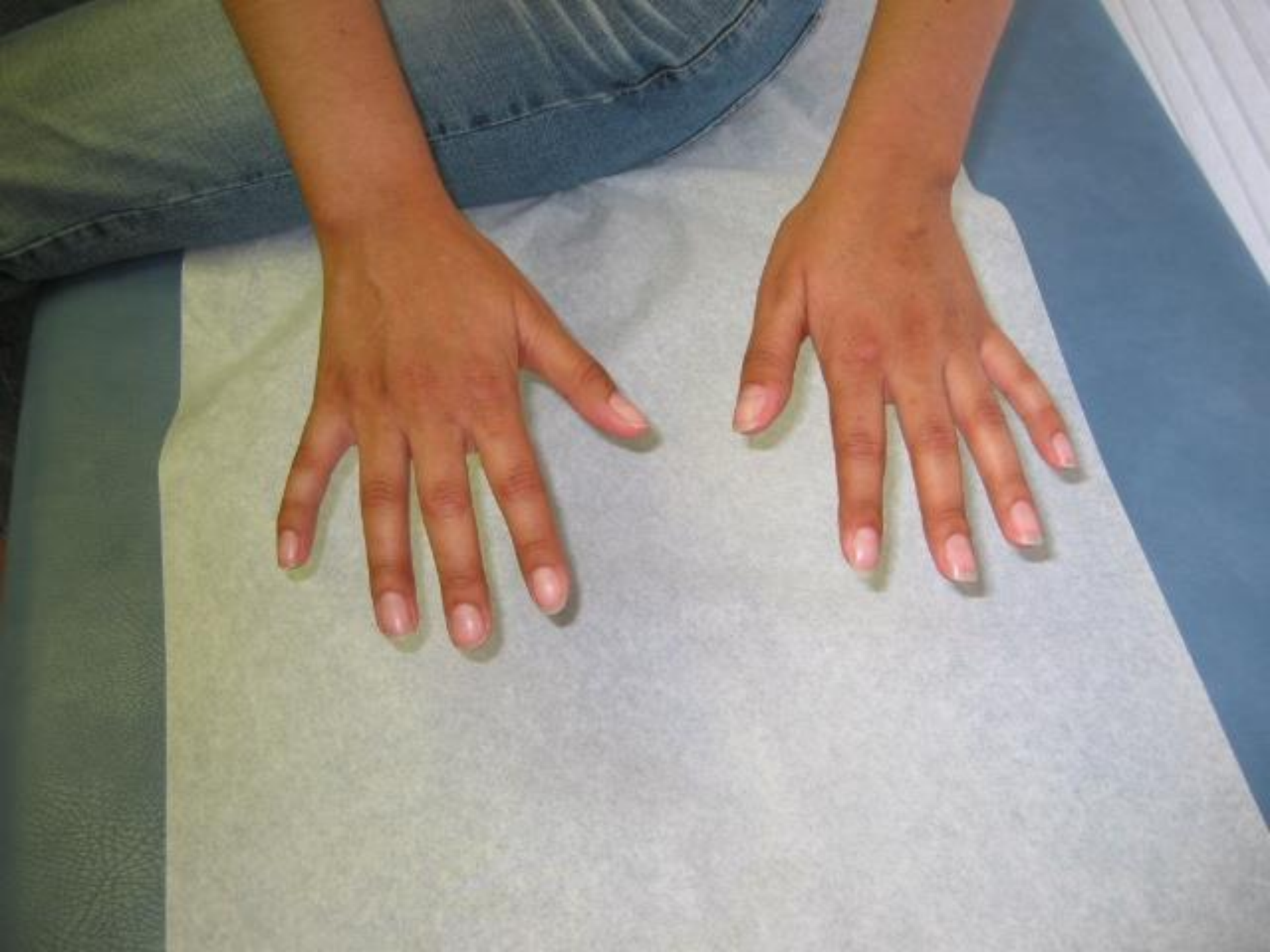
Testosterone
21-hydroxylase ★
21-hydroxylase ★
Aromatase
Aromatase
17 βHSD
Deoxycorticosterone
11-deoxycortisol
Oestrone
Oestradiol
11 βhydroxylase ★
11 βhydroxylase ★
Corticosterone
Cortisol
18-hydroxylase
18-OH corticosterone
18-OH dehydrogenase
Aldosterone
Present in adrenal and gonadal tissue

20 year old female

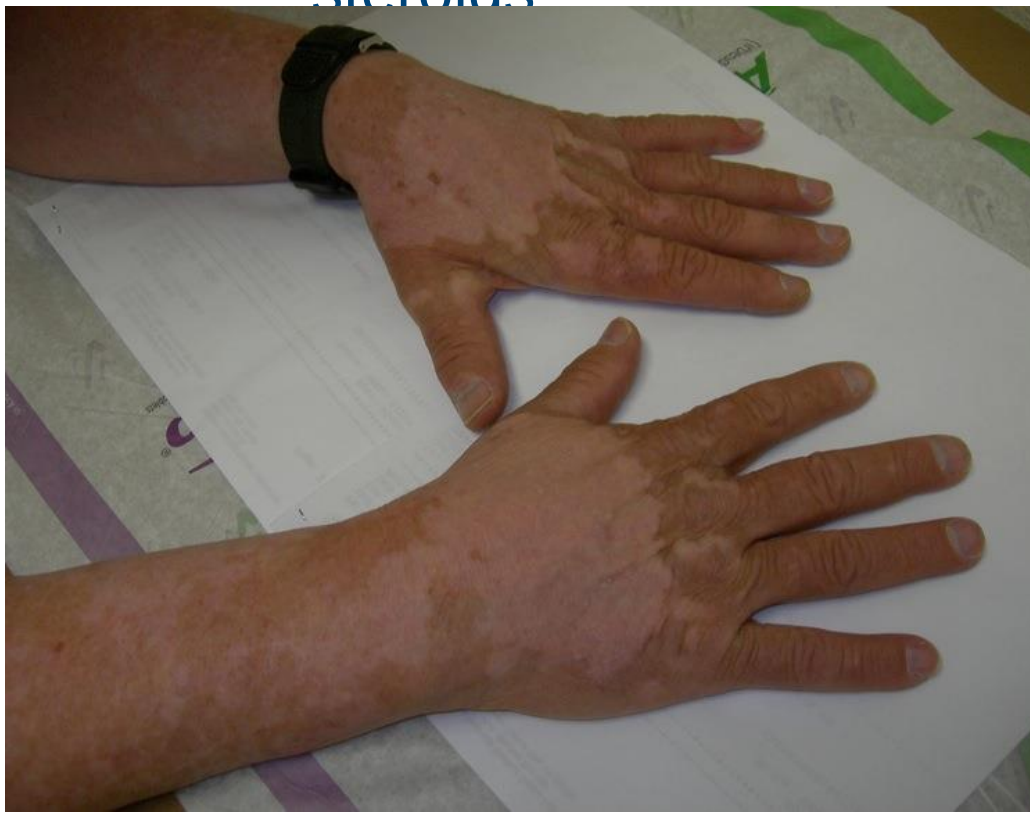
- Weight loss, easy tanning, nausea, vomiting, abdominal pain, weakness, dizzy
- BP=70/30, tan, confusion





Laboratory

- Hyponatremia
- Hyperkalemia
- Hypoglycemia
- Elevated Bun & Cr
- Vitiligo
- Deficiency of all steroids



Diagnosis

Primary Adrenal Insufficiency

Laboratory

- AM cortisol, ACTH
- Cosyntropin (ACTH) stimulation IV or IM Baseline, 30 min and 60 minute values for cortisol
- If Aldosterone drawn with Cosyntropin stimulation, response blunted

**Cortisol Goal > 18 micrograms/dl with Cosyntropin Stimulation, assuming a normal baseline cortisol

Etiology

- 80 % Autoimmune/Idiopathic
- 20 % Tuberculosis
- Other: Vascular, infectious, AIDS, trauma, mets, meds, congenital adrenal hyperplasia

Autoimmune Etiology

- Addison Disease, adrenalitis
- May be associated with other autoimmune conditions, as in Hashimoto or vitiligo

50 year old female

- Similar symptoms to index patient: low to low normal BP, fatigue weakness
- No change in skin color
- COPD

Laboratory

- Low sodium
- Normal potassium, which suggests normal aldosterone production
- Low ACTH or inappropriately normal when the end organ value is low
- Be careful with the timing of the stimulation test and blood draw for ACTH

Additional History

- History of long term steroid use IV and oral treatment
- Recent change in pharmacy
- Prednisone not renewed
- Presents with fever and lung infiltrate

Diagnosis

Secondary Adrenal Insufficiency

Etiology

- Steroid dependent
- Tumor, infection, radiation, surgery, trauma involving hypothalamic region or pituitary

Physical findings in AI

- Generalized abdominal tenderness
- Fever
- Postural hypotension
- Look for precipitating infection
- Careful with consideration for surgical abdomen
- Surgery could precipitate adrenal crisis if adequate steroids are not on board

Adrenal Insufficiency

- Electrolyte imbalance: Hyponatremia, Hyperkalemia in primary adrenal insufficiency
- Hypotension and medical crisis
- Hyponatremia without hyperkalemia in secondary adrenal insufficiency, less likely to result in adrenal crisis

Electrolyte imbalance in AI

- 85 to 90 % of patients have hyponatremia
- Mineralocorticoid deficiency results in sodium loss and volume depletion and increased Vasopressin secretion due to loss of cortisol
- Hyperkalemia in 60 to 65 % of patients
- Rare hypercalcemia

Imaging

- Consider CT of the adrenals for primary adrenal insufficiency ———small adrenals
- MRI of the brain for secondary adrenal insufficiency unless the cause is evident

Treatment at diagnosis in Crisis

- IV hydrocortisone 100 mg q 6-8 hrs wean as tolerated to daily oral dose of 25 mg daily/divided
- Saline and glucose
- Supportive and correcting precipitating factors
- Primary adrenal insufficiency: Florinef as aldosterone replacement
- If steroids < 30 days in general medical treat-ment, do not necessarily need to

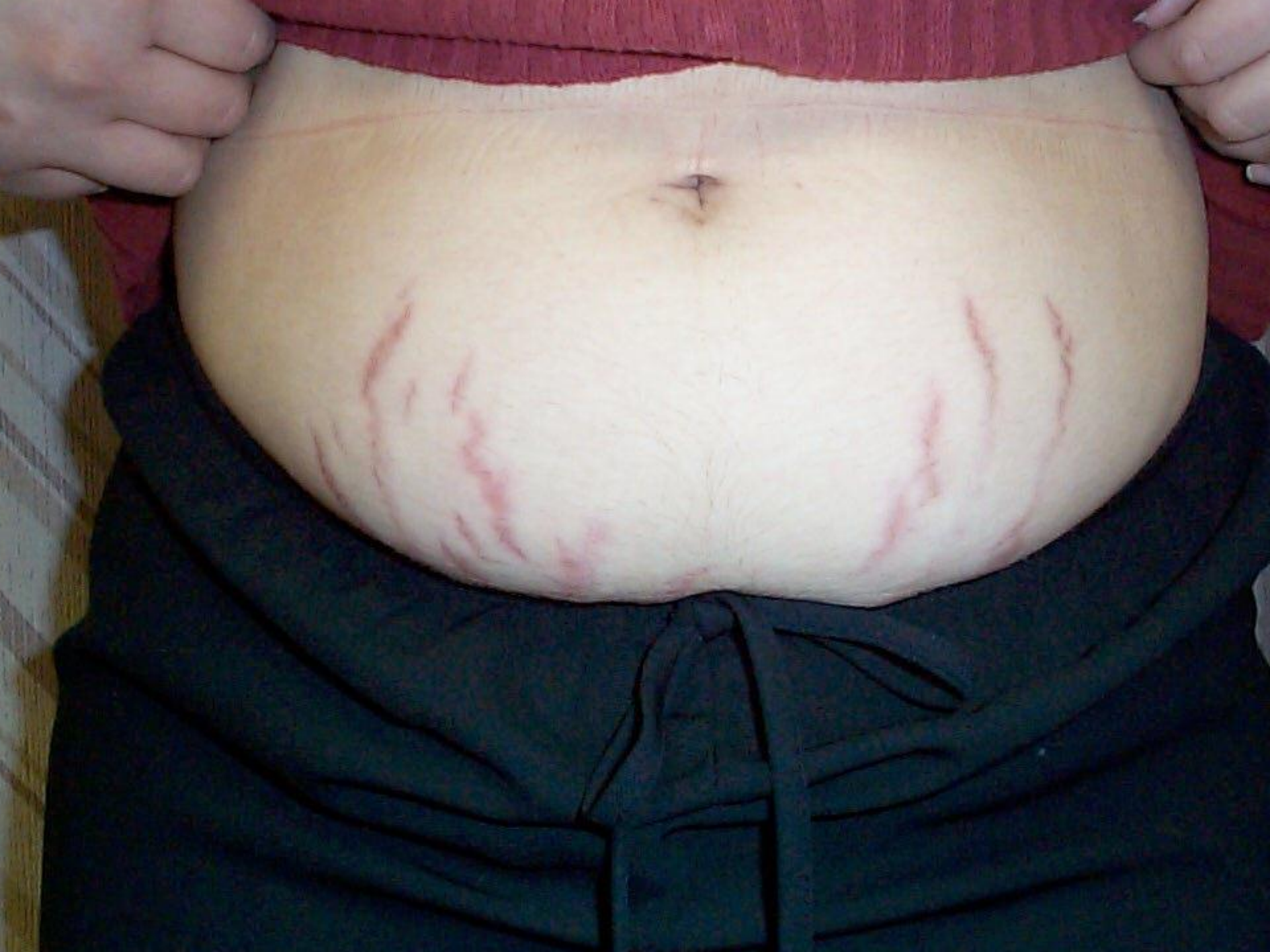
Crisis Intervention

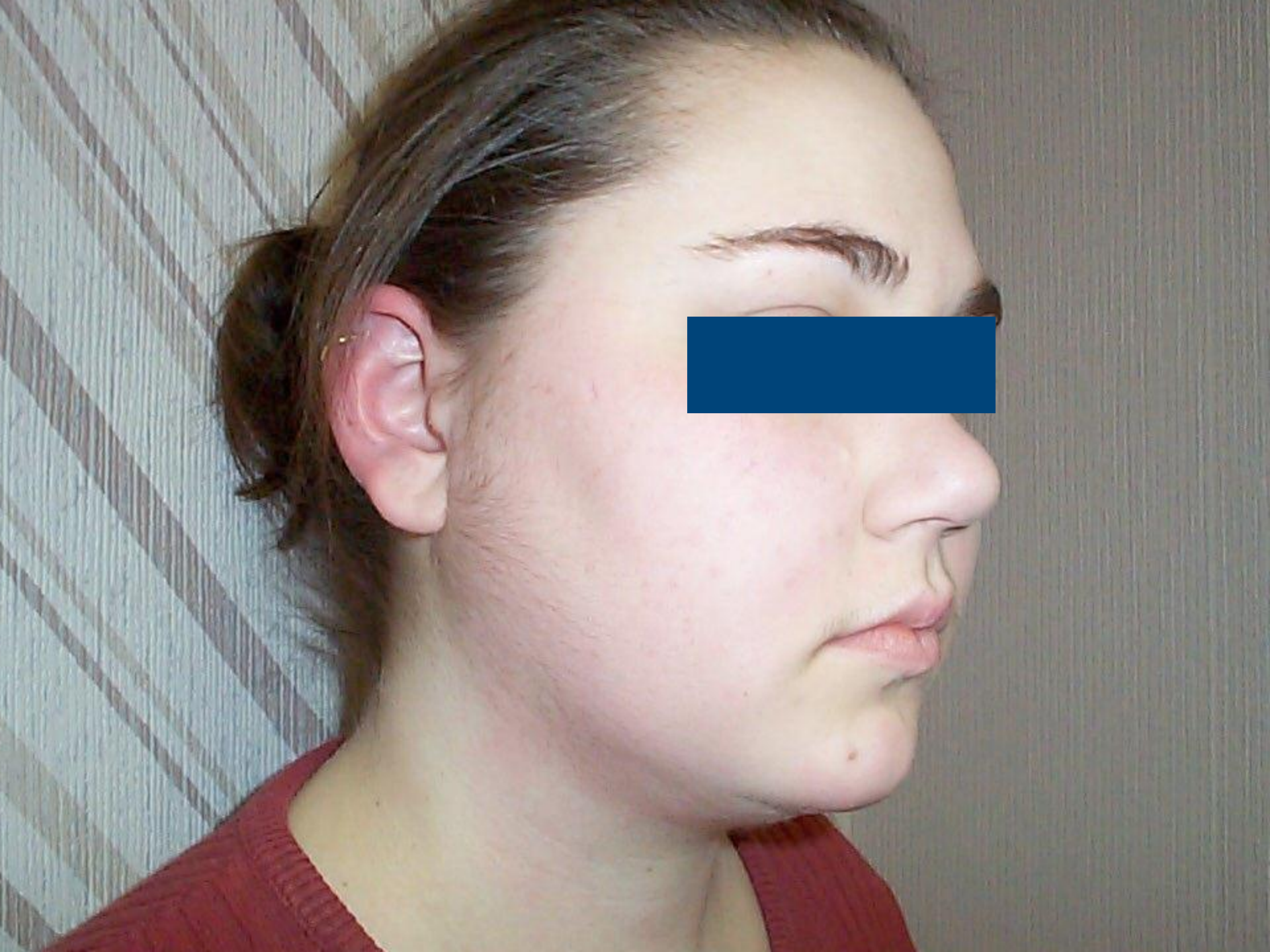
- Surgery
- Acute illness
- Additional steroids IV and/or PO
- Home illness: short course of double dose steroids
- Observe sodium, potassium and BP; Pt can follow BP at home for crisis intervention

25 Year Old Female

- Weight gain, hirsutism, diabetes, osteoporosis

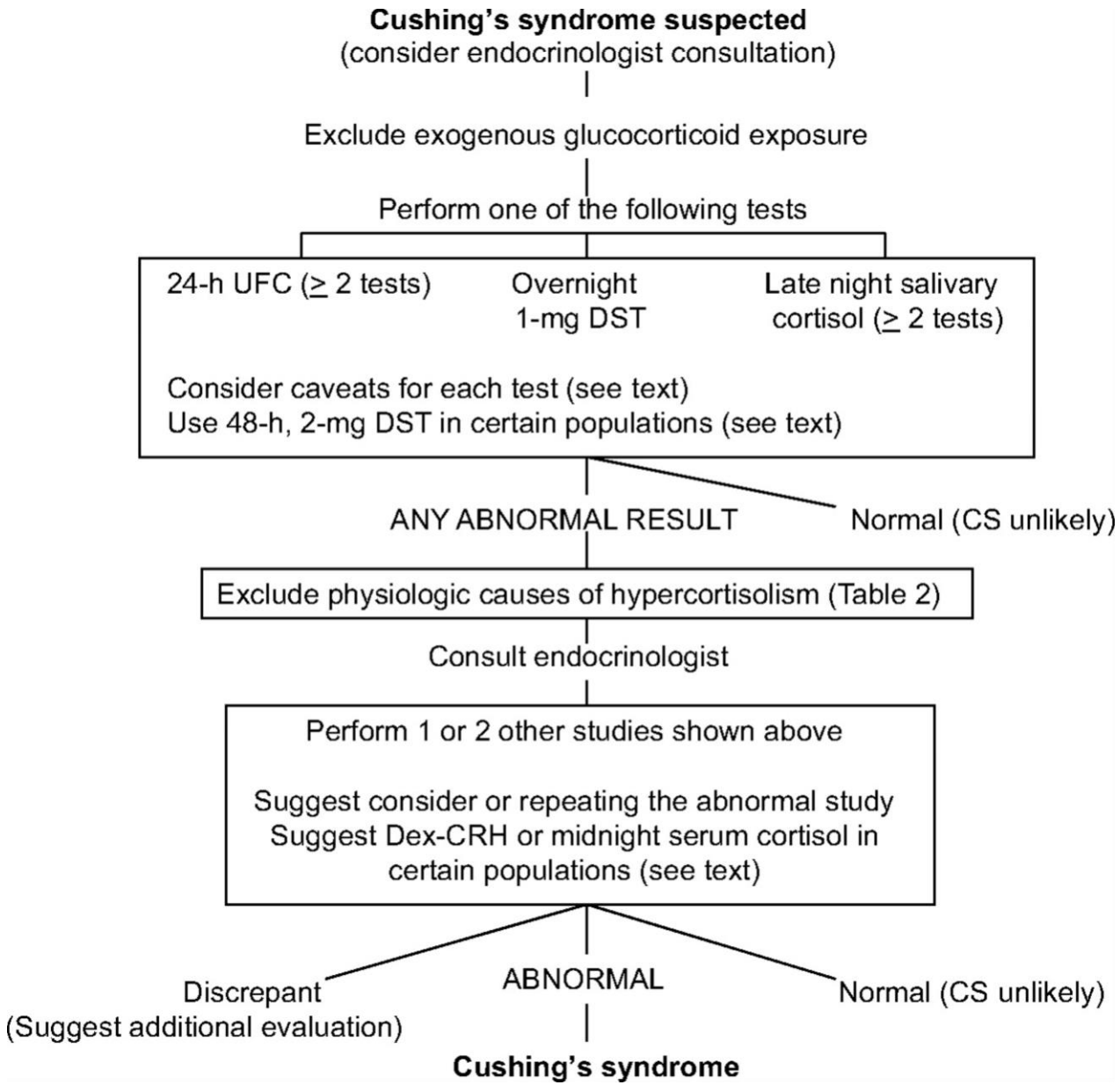
- Centripetal obesity, striae, acne, hypertension, capillary fragility, amenorrhea





Diagnosis

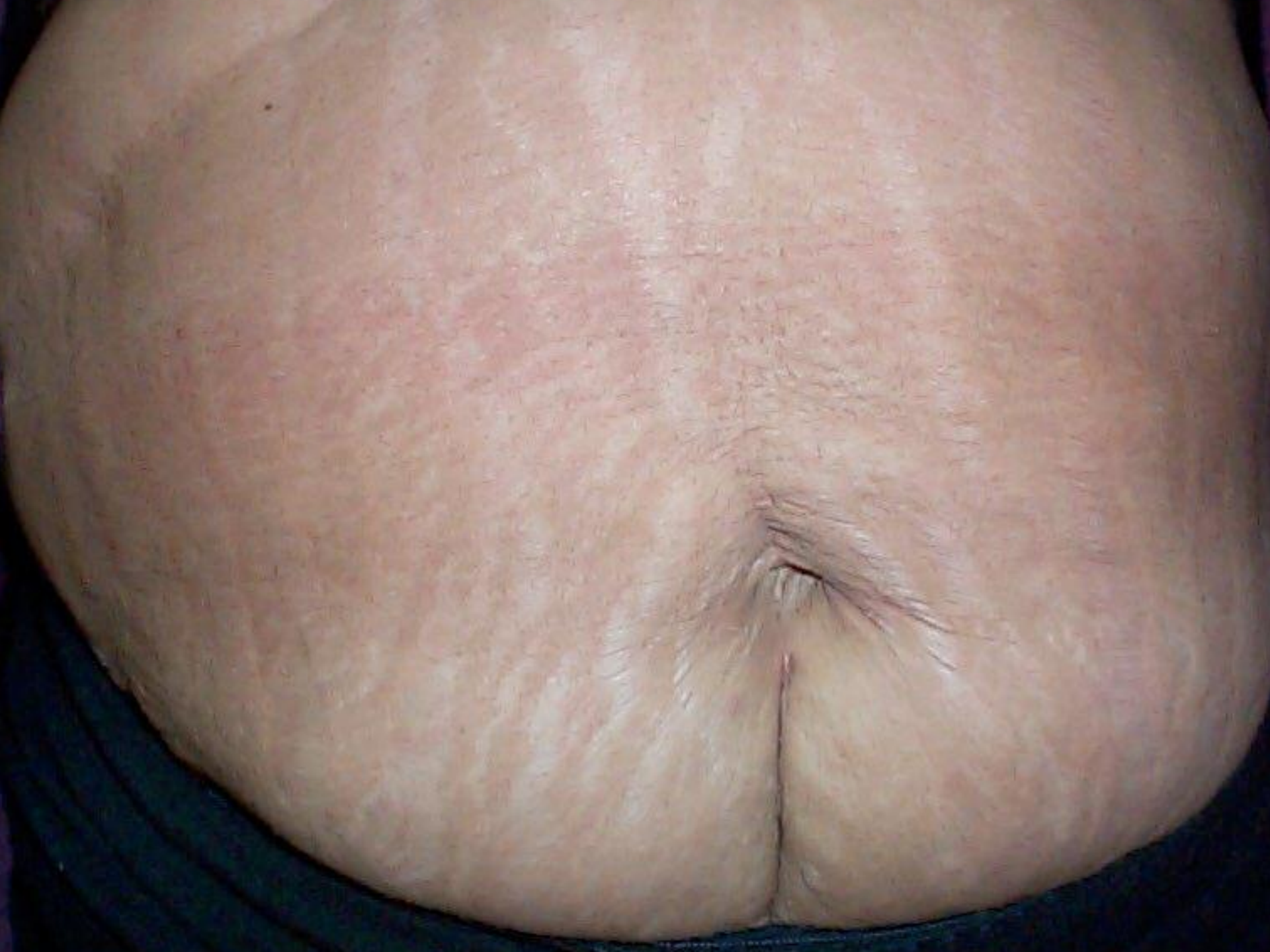
Cushing Syndrome


Cushing's syndrome suspected
(consider endocrinologist consultation)
Exclude exogenous glucocorticoid exposure
Perform one of the following tests
24-h UFC (≥ 2 tests)
Overnight 1-mg DST
Late night salivary cortisol (≥ 2 tests)
Consider caveats for each test (see text)
Use 48-h, 2-mg DST in certain populations (see text)
ANY ABNORMAL RESULT
Normal (CS unlikely)
Exclude physiologic causes of hypercortisolism (Table 2)
Consult endocrinologist
Perform 1 or 2 other studies shown above
Suggest consider or repeating the abnormal study
Suggest Dex-CRH or midnight serum cortisol in certain populations (see text)
Discrepant
(Suggest additional evaluation)
ABNORMAL
Normal (CS unlikely)
Cushing's syndrome

Laboratory

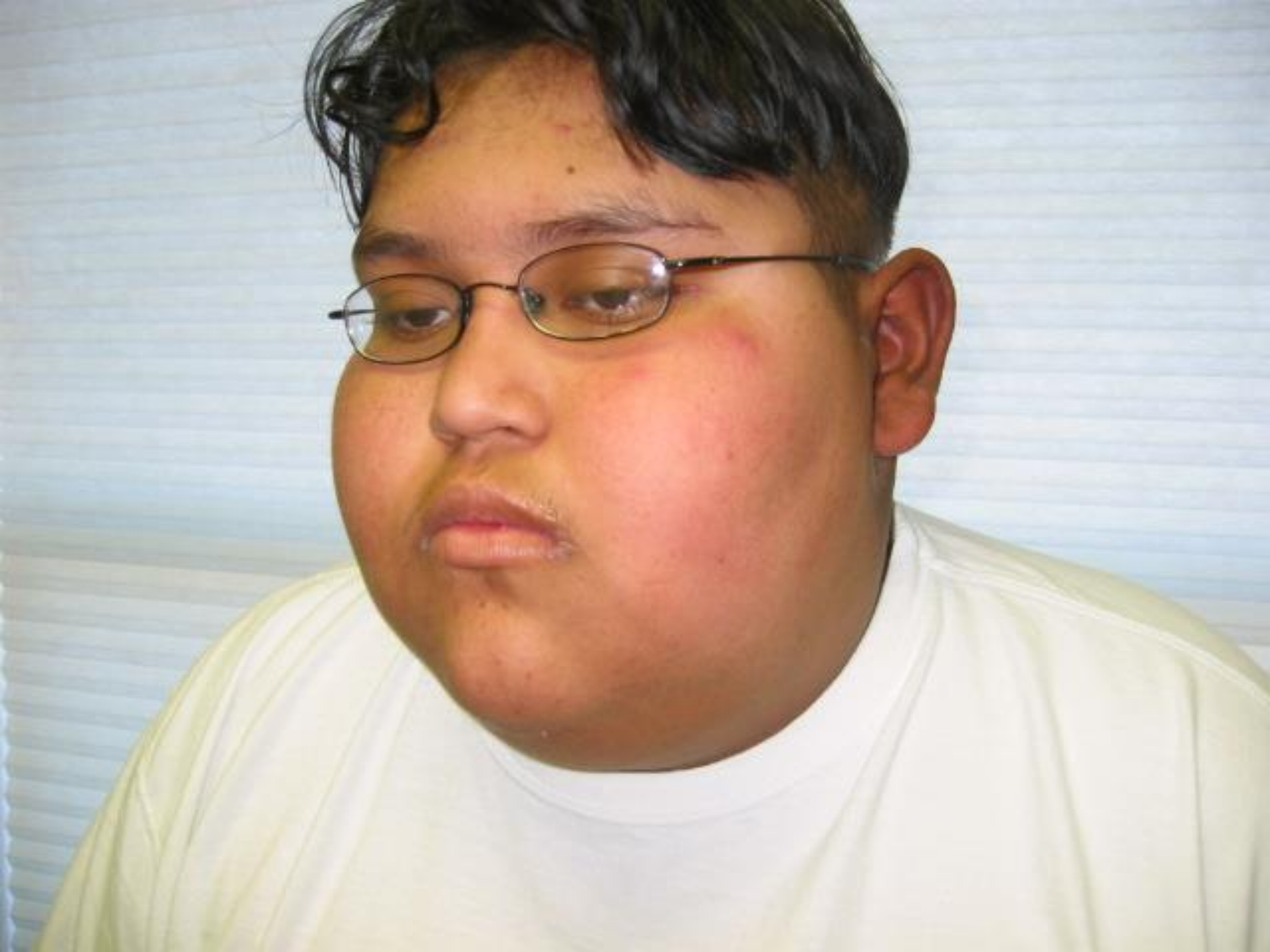
- 1 mg overnight dexamethasone suppression testing; 1 mg Dex 11 pm with 8 am cortisol next day---may identify subtle with normal urine free cortisol---goal suppression < 1.8
- 24 hour urine free cortisol
- Late night salivary cortisol
- Hypokalemia, hyperglycemia
- Some false positives

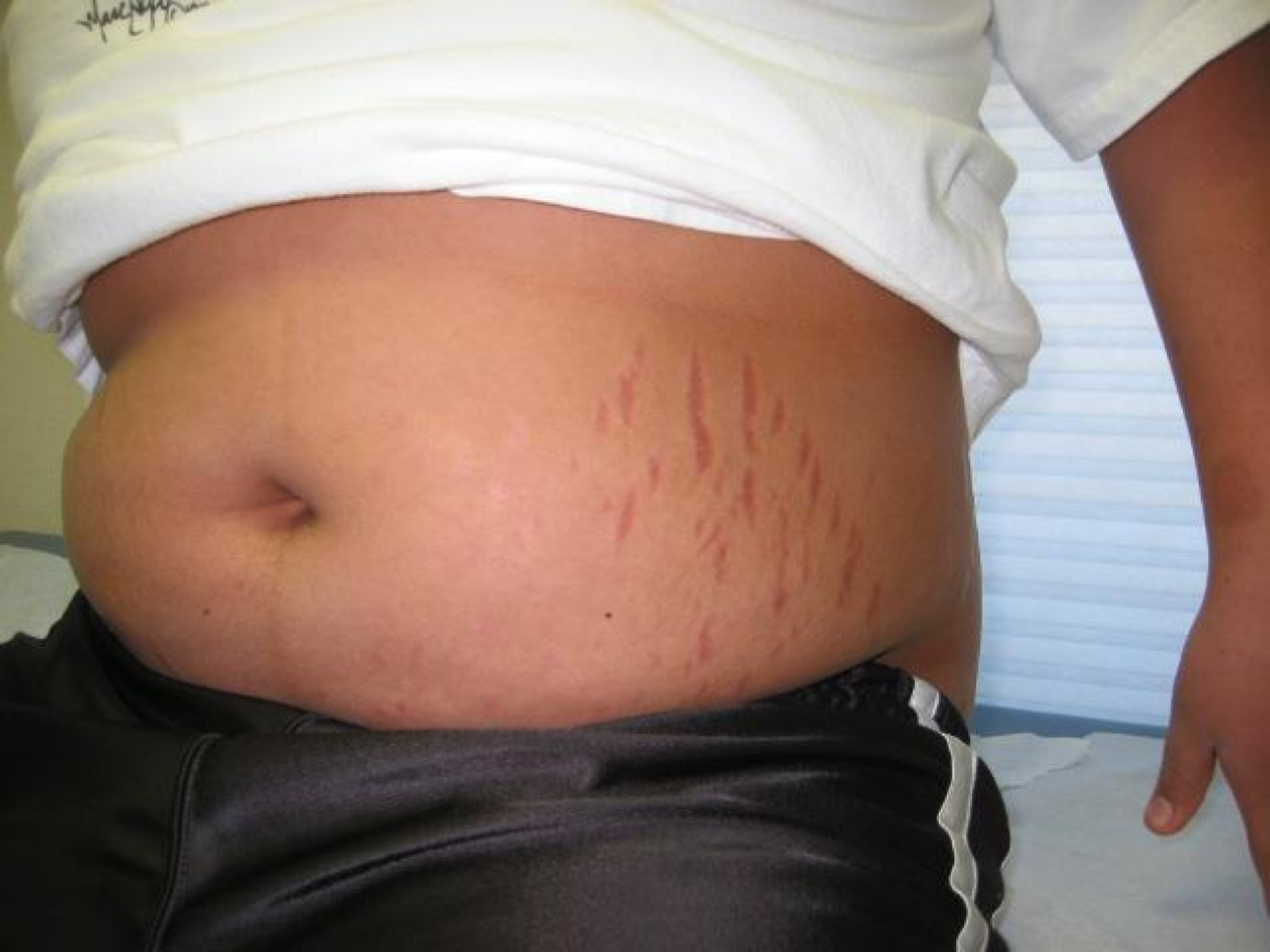
Pregnancy Striae



Differential Diagnosis

- Cushing disease: Cushing syndrome due to pituitary adenoma/high ACTH---dependent
- ACTH Independent vs ACTH Dependent
- Exogenous steroids
- Adrenal adenoma or hyperplasia
- Ectopic: lung tumor





Differential Diagnosis

- Cushing disease and ectopic have higher ACTH>>>>ACTH Dependent
- Adrenal disease is ACTH independent
- Clarification required with additional dexamethasone testing including urinary testing

Imaging

- Cushing disease: MRI of the pituitary
- Cushing syndrome: CT or MRI of (adenoma vs hyperplasia) adrenals
- Ectopic: localize source

Treatment

- Pituitary: surgery, radiation, anti-adrenal drugs
- Ectopic: surgery, drugs
- Adrenal: surgery, drugs

Adrenal Carcinoma

- Metastatic at diagnosis
- Presents with weight loss
- Rapid onset
- Typical excessive activity of steroidogenesis pathway, not typical insufficiency

35 Year Old female

- Hypertension
- Hypokalemia
- Thin
- Metabolic alkalosis

Diagnosis

Hyper-aldosteronism

Hyperaldosteronism

- Biochemical work-up first
- Low renin/high aldosterone is primary
- High renin/high aldosterone is secondary
- Elevated 24 hour urine aldosterone on high sodium diet and off diuretics
- Saline Suppression Testing

Hyperaldosteronism

- Adrenal adenoma (Conn Syndrome) “APA” Aldosterone Producing Adenoma
- Idiopathic Hyperaldosteronism “IHA” with bilateral disease

Secondary Hyperaldosteronism

- Sodium restriction
- Renal disease
- High Potassium intake
- Pregnancy
- Diuretics

Localization testing

- Cat Scan
- Nuclear imaging with Iodocholesterol
- **Adrenal venous sampling—Gold Standard**

Adrenal Venous Sampling Summary

RE: Male DOB: 1942

	Aldosterone (ng/dL)	Cortisol (ug/dL)
Basal:		
Right adrenal vein	1	4.3
Left adrenal vein	221	10.2
Peripheral Arm	12	12.3
POST ACTH:		
Right adrenal vein	4	108.1
Left adrenal vein	16430	>150
Peripheral Vena Cava	71	14.4
Peripheral Femoral Vein	46	18.9

Treatment

- Aldosterone producing adenoma: surgery; takes 6 months for final HTN results, may have underlying essential HTN but hypokalemia should resolve; Spironolactone in patients with poor surgical risk

- Bilateral adrenal disease: restrict sodium, spironolactone use, no surgery

40 Year Old Male

- Hypertension unresponsive to meds
- Normal electrolytes
- Thin
- Headache, palpitations

Diagnosis

Pheochromocytoma

Laboratory

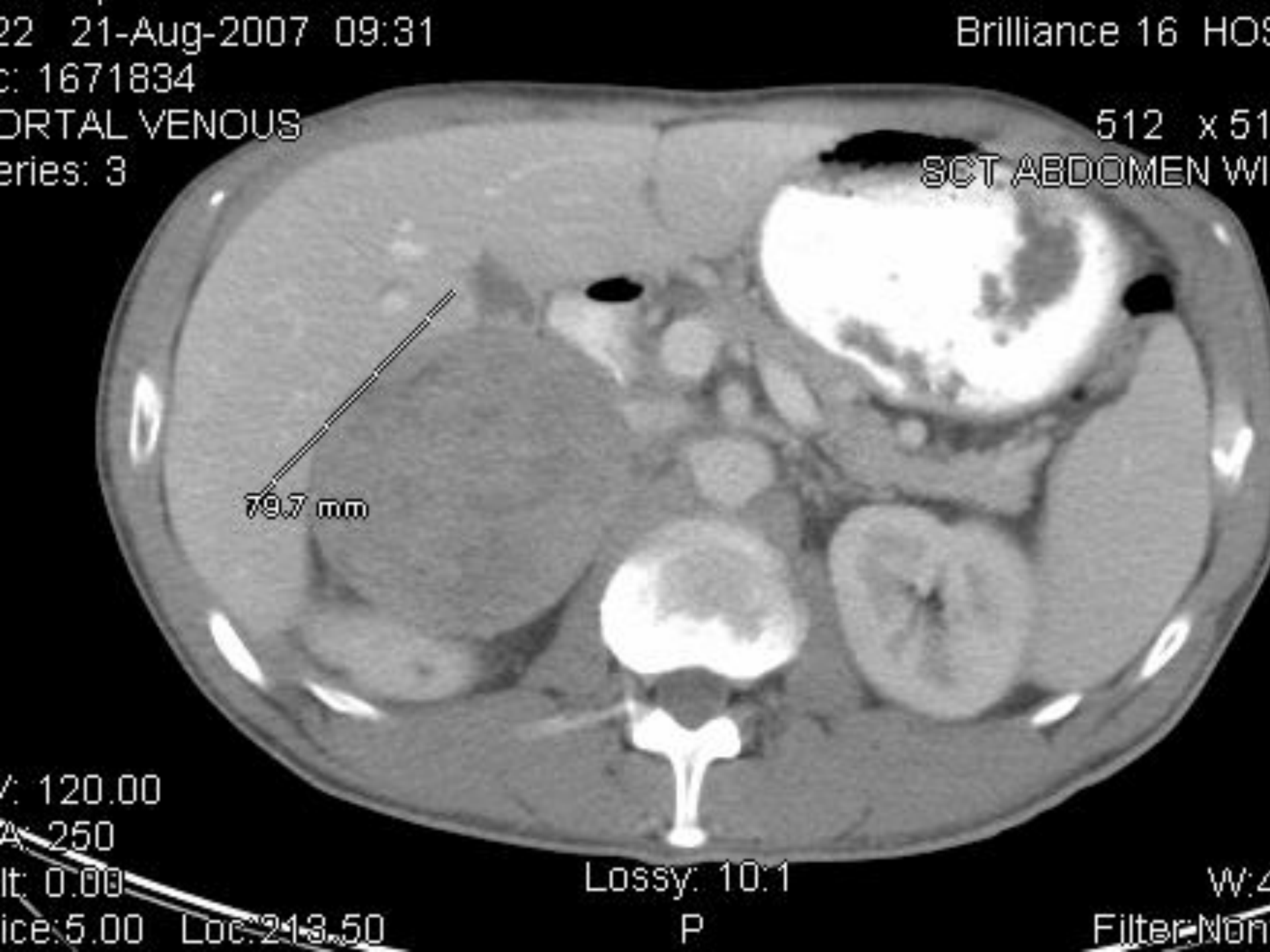
- Check 24 hour urine fractionated catecholamines, fractionated metanephrines, VMA
- 24 hour urine testing off meds if possible
- Some endocrinologists recommend serum catecholamine/metanephrine testing

Imaging

- MRI or CT: MRI may help with difference in signal intensity T1/T2---bright signal in pheo
- MIBG (Metalogobenzylguanidine) nuclear imaging tracer concentrates in catecholamine producing cells

Treatment

- Alpha blockers preferred
- Avoid Beta Blockers, which can precipitate a pheo crisis without alpha blockade on board
- Avoid adrenal biopsy of a lesion that is not yet evaluated for pheochromocytoma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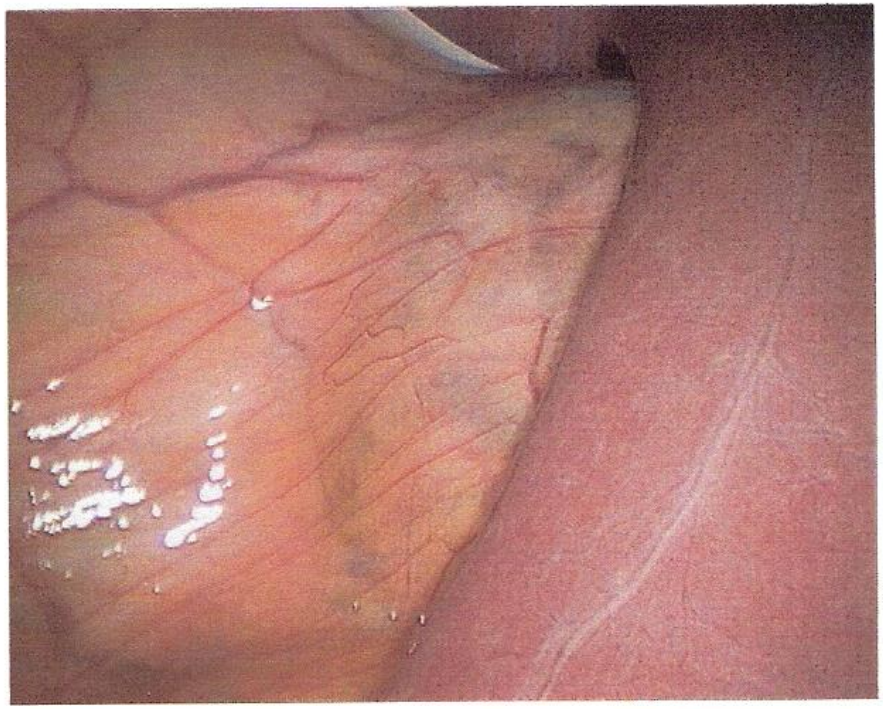

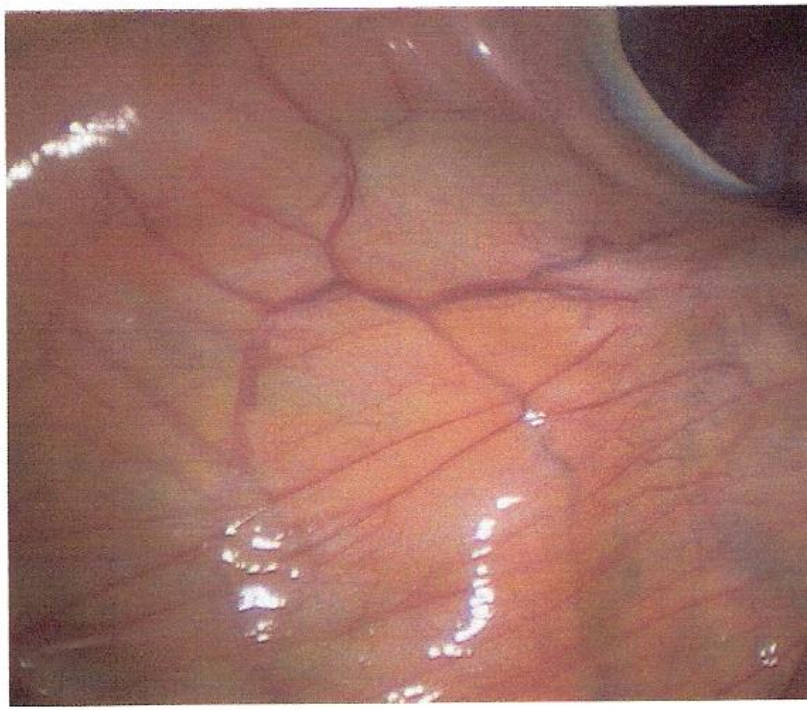

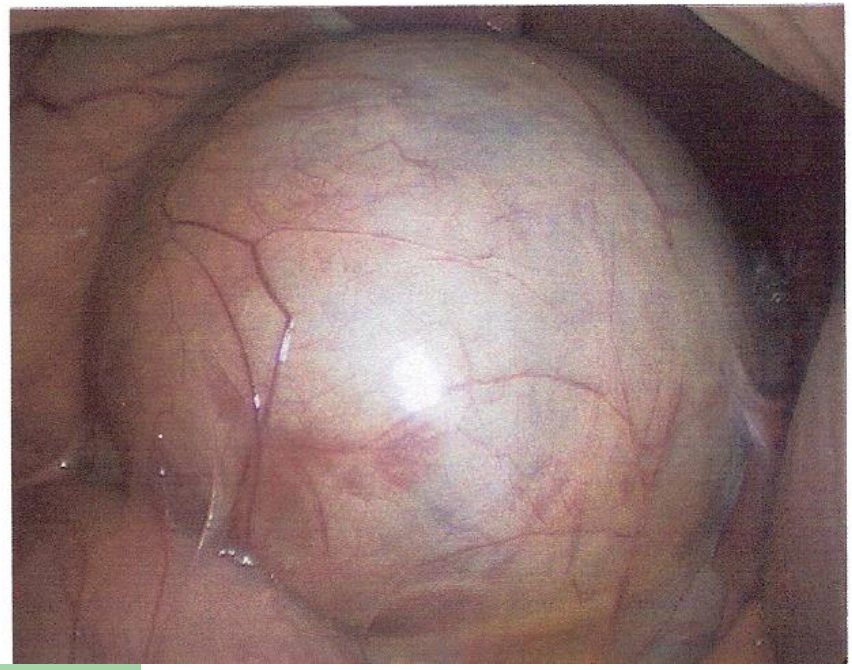

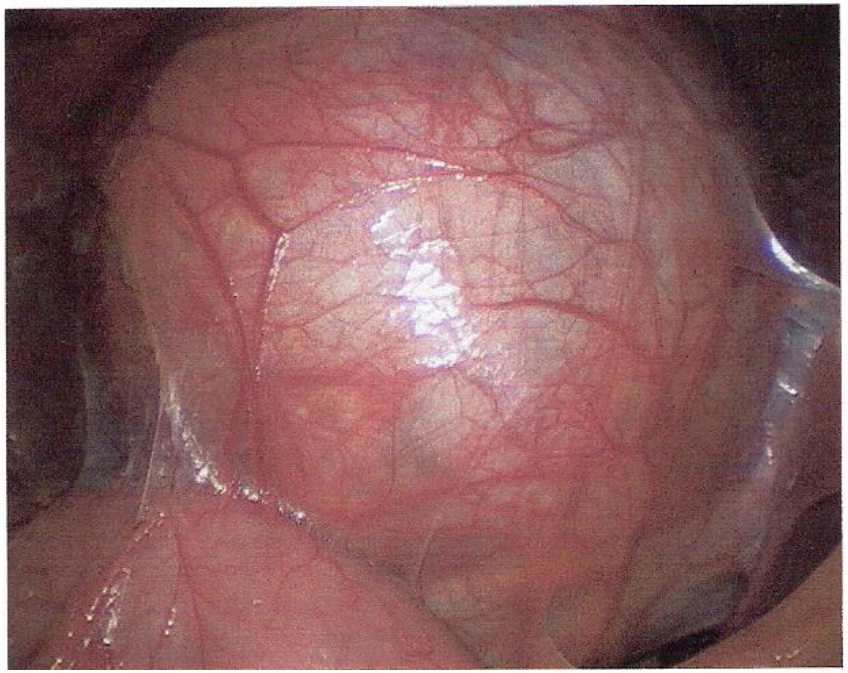

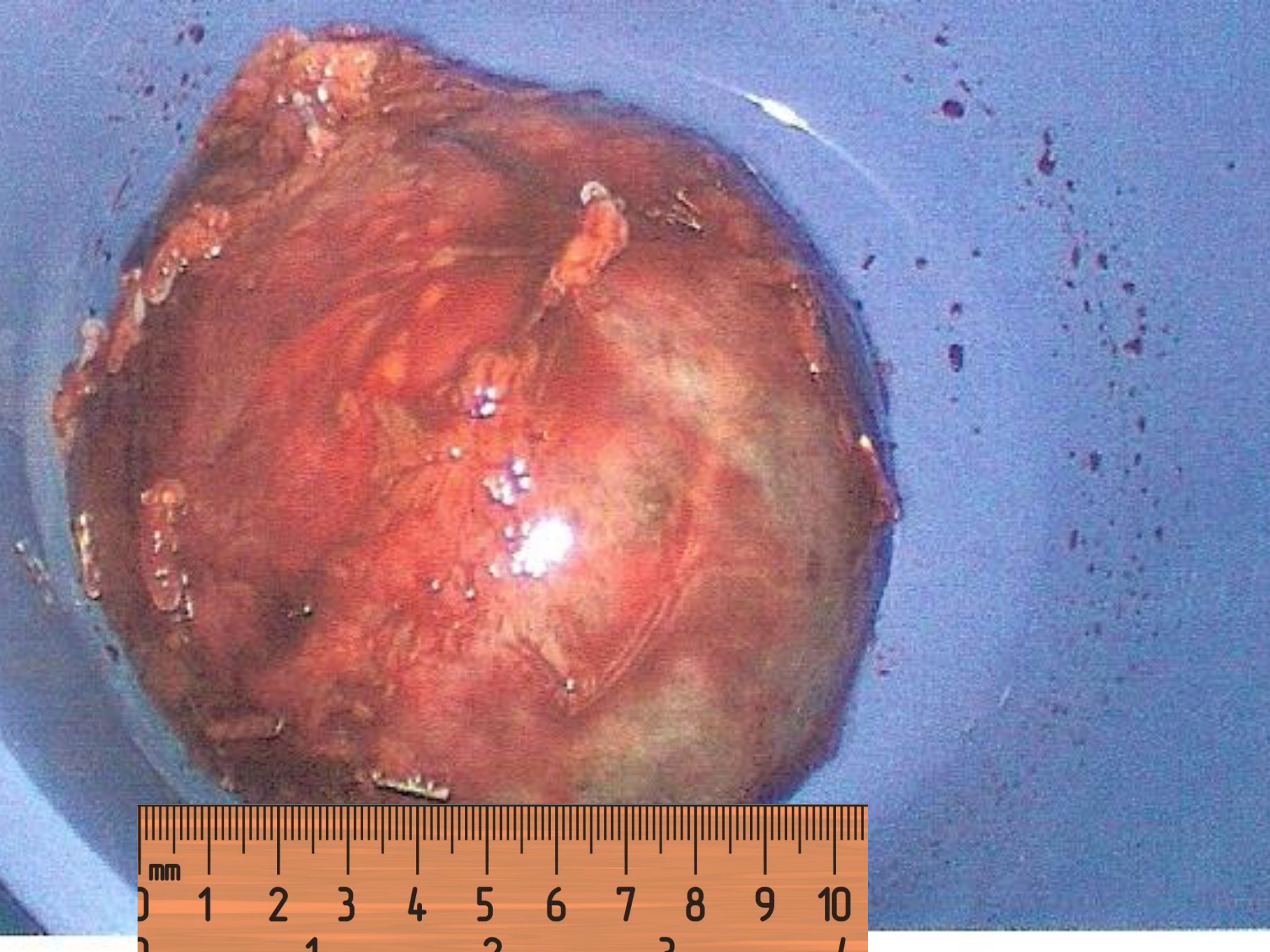
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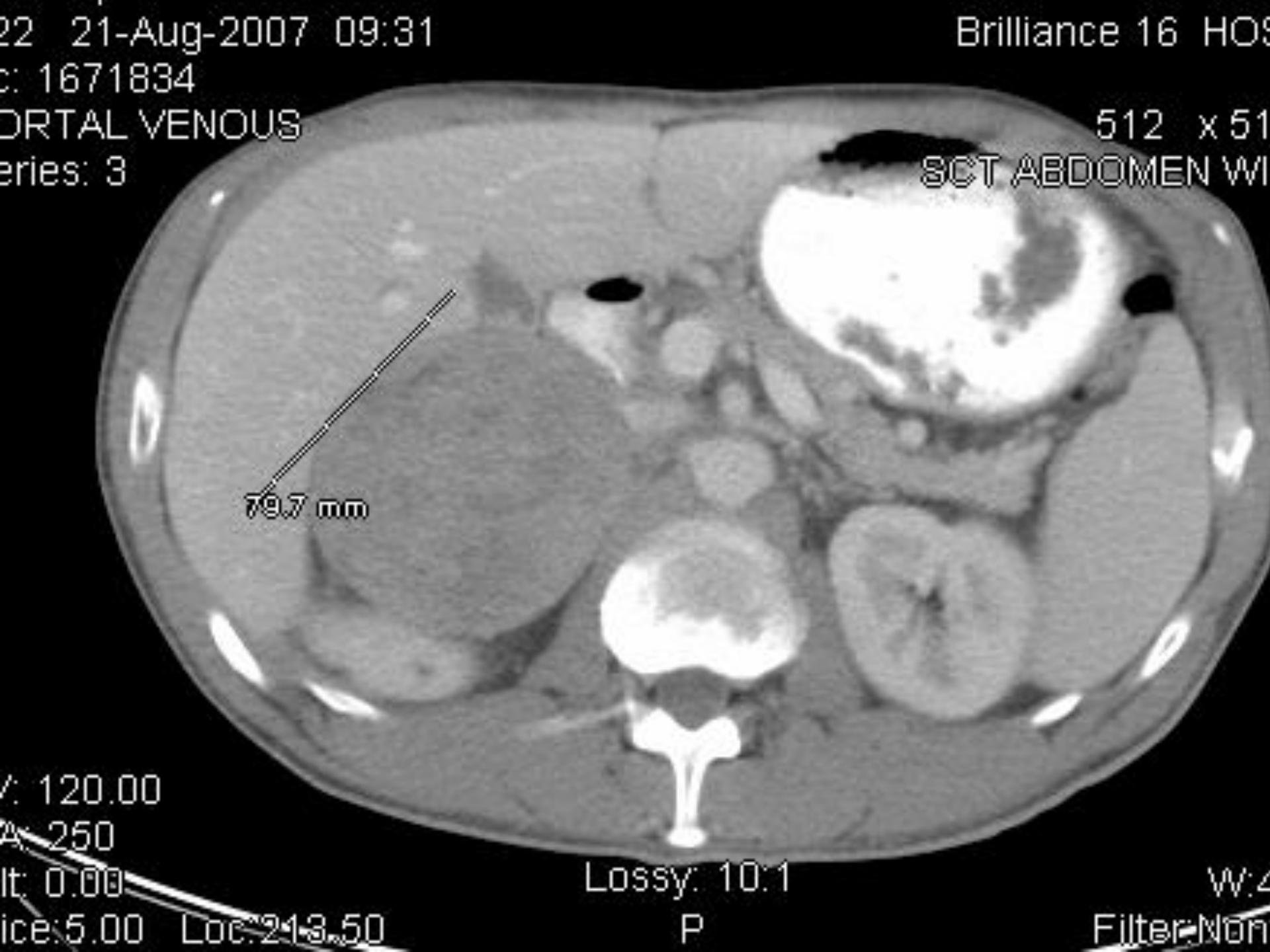
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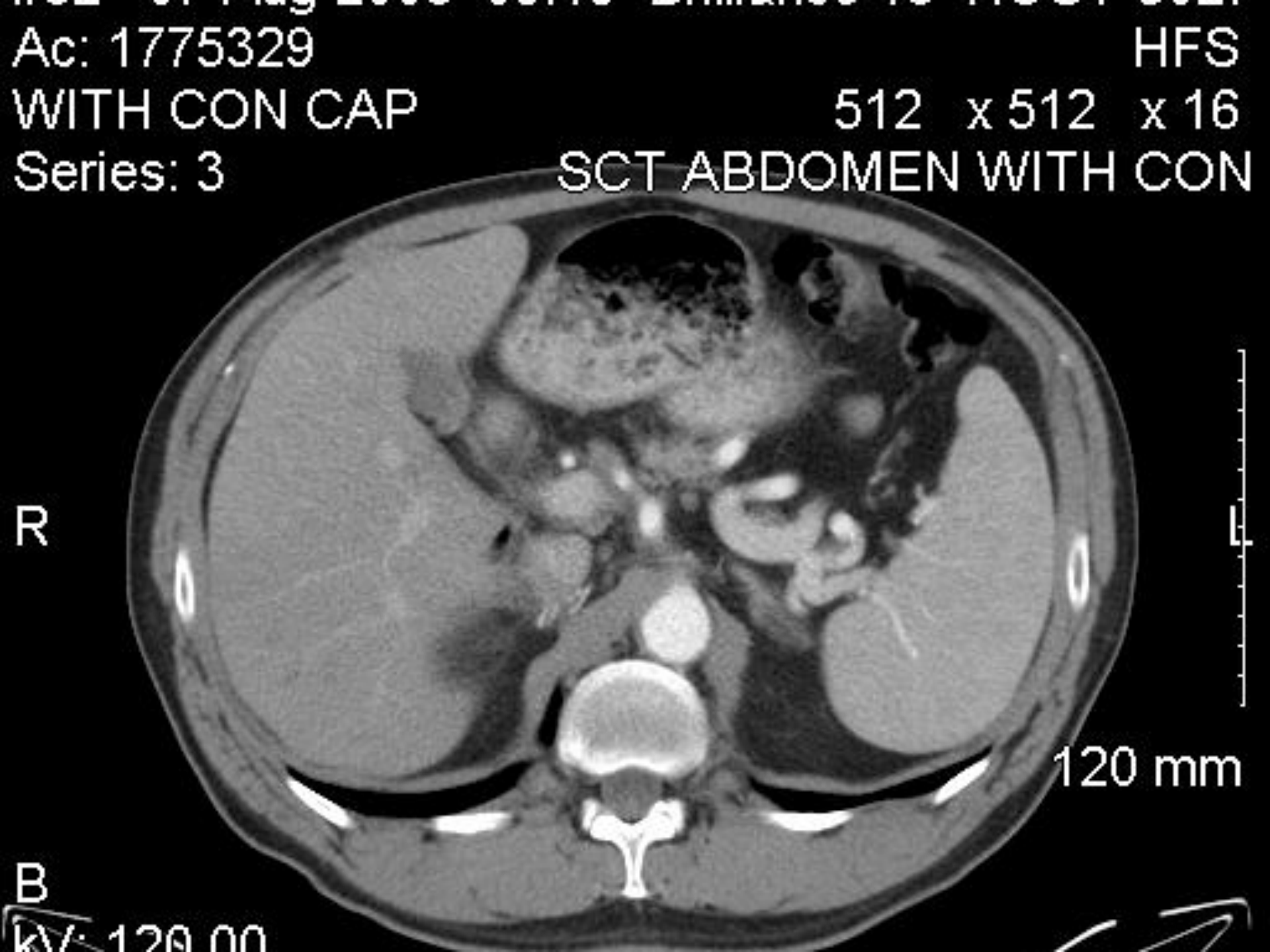
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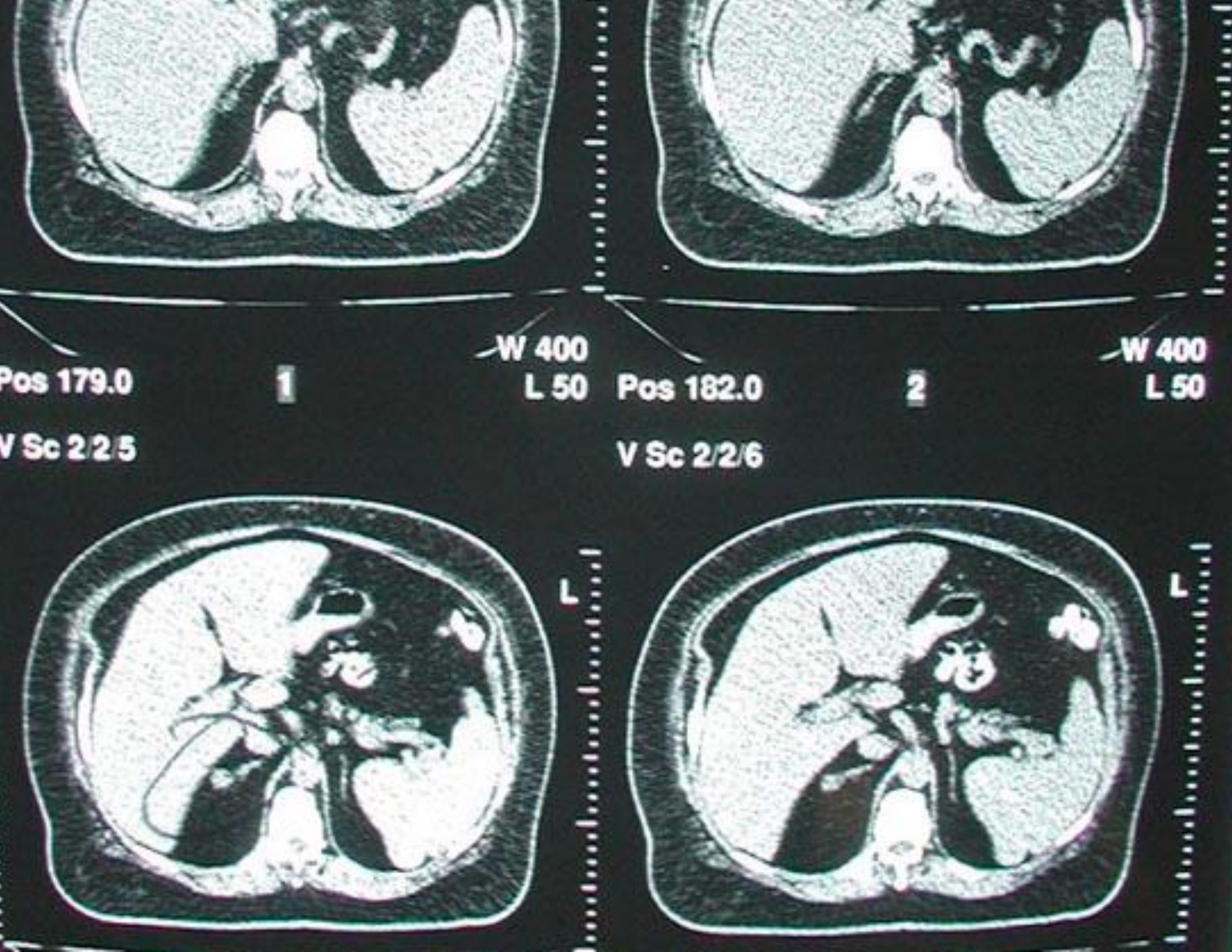
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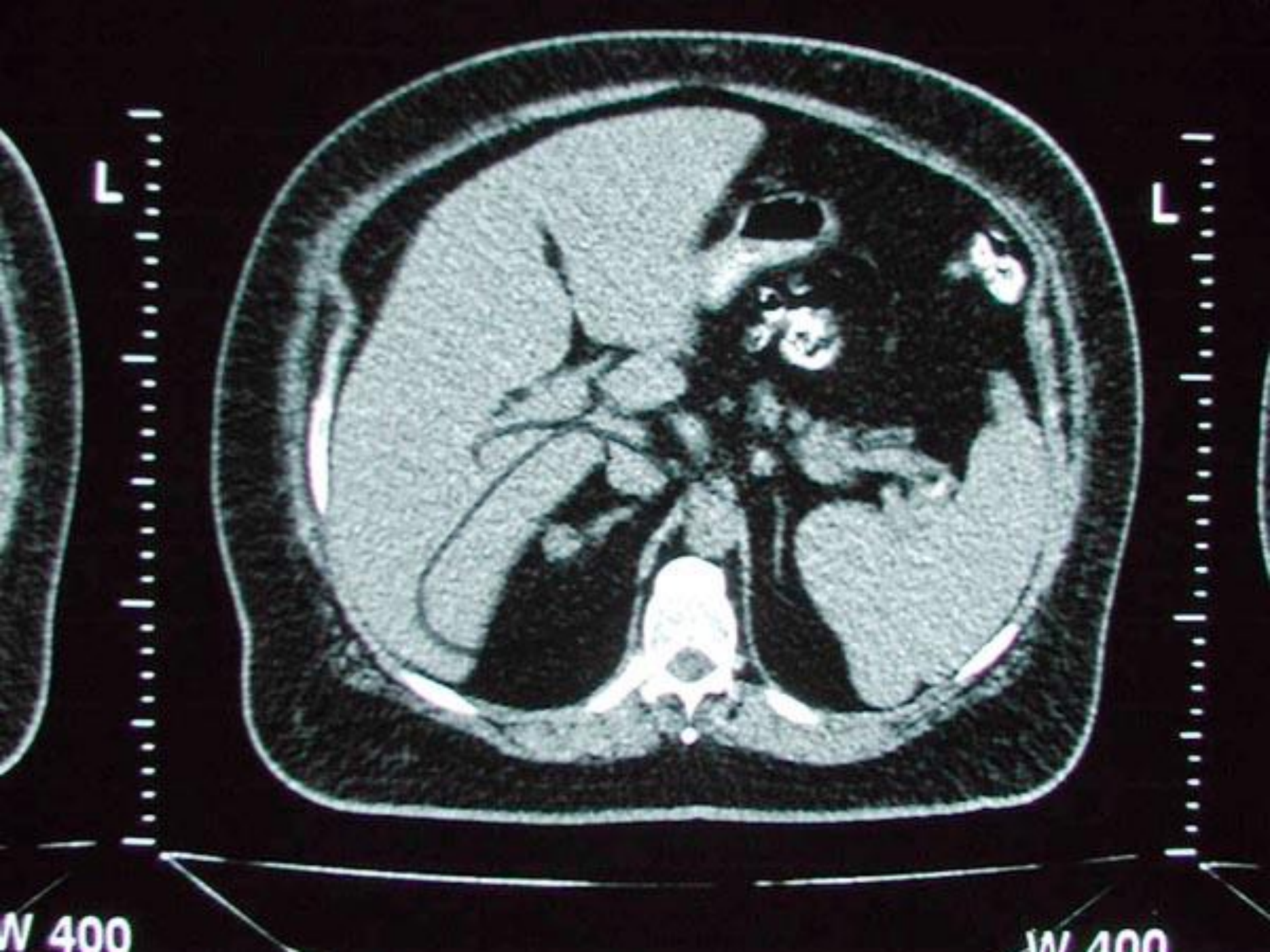
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Incidental Adrenal Adenoma

- Benign adenomas common
- Avoid imaging until biochemical diagnosis
- Evaluation important with coexisting HTN, hypokalemia, hirsutism

Adrenal Incidentaloma

- Lesions discovered “inadvertently in the course of diagnostic testing or treatment for other clinical conditions that are not related to the suspicion of adrenal disease”

Prevalence

- In autopsy series 2.1 %
- More identified with better imaging
- Prevalence of 4.3 % in patients with a previous diagnosis of cancer
- Higher with aging at 7 % in 70 +
- More lesions in women—related to who is being tested

Causes

- Pathology: Cancer patients ¾ mets, No history of cancer 2/3 benign
- 70 % non-functioning in patients without endocrine symptoms
- 5-10 %-----Cushing Syndrome, subclinical

Natural History of lesion size

- 25 % of lesions larger than 6 cm represent adrenal cancer
- Up to 25 % of adrenal lesions may grow 1 cm, but the significance of size change is not known
- Adrenal Cancer rapid growth “doubling time”

Natural History of function

- Up to 20 % may develop a functional component
- Development of function more common in larger neoplasms (3 cm)---this evidence can depend on study follow-up length and methods
- Less than 3 cm neoplasms rarely change in function

Adrenal Incidentaloma Diagnosis

- Function
- Surgical resection vs non-surgical treatment
- Malignant vs benign