62 y.o. female with hirsutism

HPI

- 62 y.o. female who has been following in the clinic for postsurgical hypothyroidism, pituitary microadenoma on routine f/u visit noted with significant hirsutism

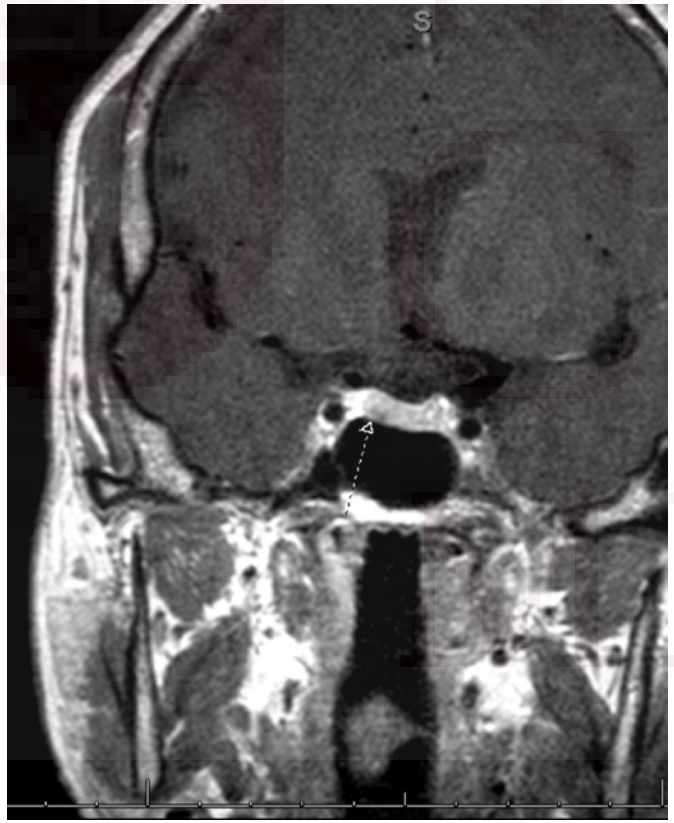
HPI

- Noted new facial hair growth 1-2 years ago accelerated over last 3-6 months
- Now requiring weekly waxing
- Denies significant worsening hair growth in other areas (thighs, pubic, arms, breast/chest etc.), maybe some over lower legs and perineal area
- Deepening of the voice noted years ago (after thyroidectomy 2014) and was investigated, no change since
- Denies thinning of scalp hair
- More oily skin, + acne
- Clitoral enlargement noted ~2 years ago when became sexually active again
- No changes in sex drive

Other pertinent history

- Menstrual periods regular, however heavy
- Last MP 12/1997
- Hysterectomy 3/1998 due to excessive bleeding
- G1P0 (abortion) did not try more
- In her 30s was told she has ovarian cysts at 2 different occasions

Past medical history:



- **Hypothyroidism:** diagnosed with multinodular goiter in 2005. She is s/p total thyroidectomy with Dr. Angelos on 4/1/14. Benign pathology. LT4 was tapered down from 137 mcg post op to 88 mcg recently after presentation with thyrotoxicosis

- **Pituitary microadenoma**: initially noted at 6 mm in 2005 with no significant changes until 2015 when it was measured at 3 mm.
- repeat MRI 2017: punctate T2 hyperintensity within the left aspect of the anterior pituitary gland, measuring 3 x 3 mm. also possible relative hypoenhancement along the inferior aspect of the right lateral anterior gland measuring 2-3. there is a slightly heterogeneous enhancement pattern of the gland.

she had normal ACTH stimulation test, normal FSH, IGF-1, and prolactin. normal visual field testing in November 2013. Her prolactin was mildly elevated in 2005. She was never treated with a dopamine agonist

PMHx

- Migraine HA
- Secondary hyperparathyroidism
- ?RA on steroids/methotrexate/Plaquenil at some point
- Depression/anxiety
- Rosacea/acne vulgaris
- CKD III
- Sx: thyroidectomy 2014, hysterectomy 3/1998

Family history

- Mother with Hx of migraine, depression, DM II, pancreatic cancer metastasized to Ovaries
- Father: prostate CA, asthma
- PGM: pancreatic Ca
- Breast Ca in multiple fam members maternal side

ROS

- Constitutional: no fever/chills, night sweats, denies weight loss, **+ fatigue, + anxiety**
- HEENT: no blurred or double vision, no dysphagia, **+ hoarseness**
- RESP: no dyspnea, no cough or increased WOB
- CV: denies CP/palpitations, LE edema
- GI: no abdominal pain/N/V/diarrhea, no constipation
- GU: no urinary symptoms, **+ vaginal dryness** (Tx with estrogen pills)
- MSK: + joint pain (chronic OA)
- Neuro: **+ HAs**, no paresthesia's, no weakness
- Endo: no cold/heat intolerance, **+ oily skin**, no hair loss
- Psych: + anxiety/depression, not suicidal

Physical exam

- Vital signs: Blood pressure 132/84, pulse 91, height 177.8 cm (5' 10"), weight 89.6 kg (197 lb 9.6 oz), BMI 28.4
- Const: NAD
- Generally: a well-appearing female in no acute distress.
- Neck - thyroidectomy scar
- Pulm - CTAB
- CV - no LEE
- Neuro - non focal, Axox3
- MuscSkelet - nl ROM
- GI - soft abdomen, not distended
- Skin - coarse hair chin and sideburns, acne

medications

- albuterol, mometasone, singulair, Flonase
- azelaic acid (AZELEX) 20 % Top cream
- cetirizine HCl, fexofenadine HCl
- chlorthalidone (HYGROTON) 25 mg Oral tablet
- clindamycin (CLEOCIN-T) 1 % Top topical gel, topical metronidazole, econazole, sulfacetamide Na-sulf
- clonazepam 0.5 mg Oral tablet
- cyclobenzaprine (FLEXERIL) 10 mg Oral tablet .
- escitalopram oxalate (LEXAPRO) 20 mg Oral
- estradiol 10 mcg VAGINAL tablet
- levothyroxine 88 mcg Oral tablet
- omeprazole (PRILOSEC), Zantac
- tramadol (ULTRAM) 50 mg Oral tablet

Thoughts on d/d and workup?

Lab

	9/23/2019 1541
ENDOCRINOLOGY	
ACTH	
BHCG, Plasma, Quant.	*1.4 **
Cortisol	*5.9 **
Estradiol (Endo Lab)	
FSH	*48.0 **
LH	*43.6 **
Prolactin	
Prolactin	*22.70*
SMC/IGF1 Stim Panel	
Te Binding Globulin	*84*
Calculated Free Te...	*34 **
Total Testosterone	*217* ▲
Test Information	*The Total Test... **
FSH	
ACTH	*25.9*
DHEA-S	*35.7*
IGF1 LC MS	

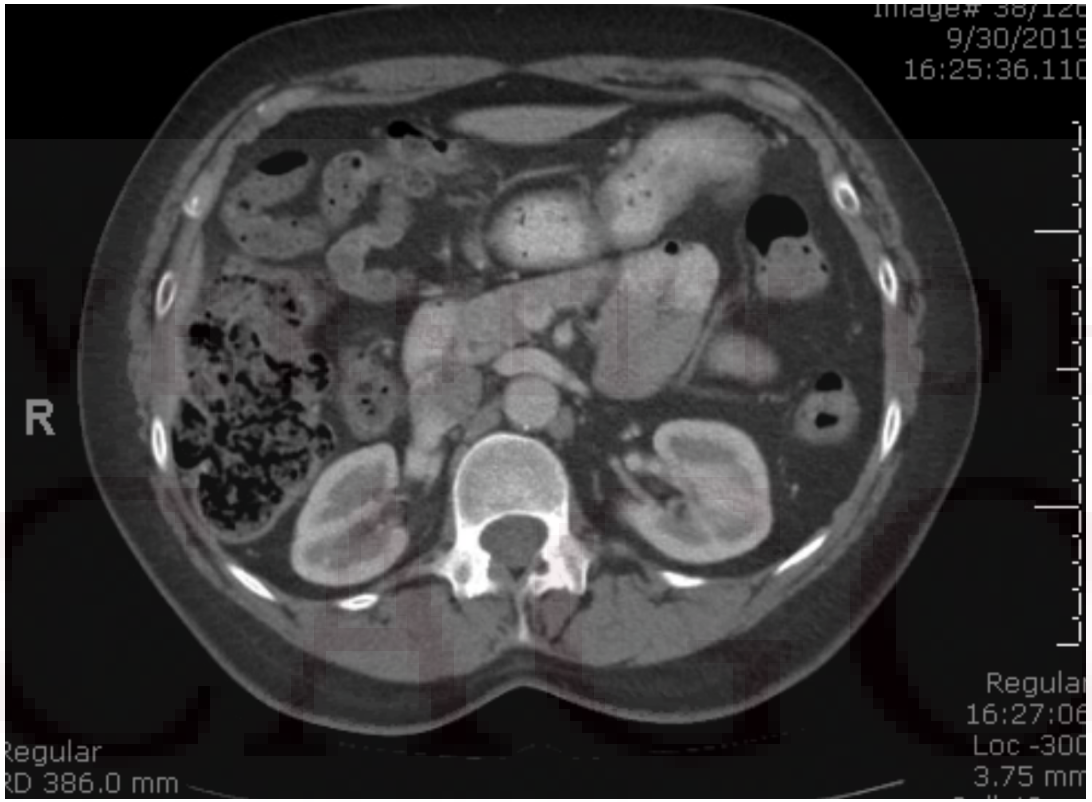
Component	Value	Ref Range & Units
IGF1 LC MS	98	35 - 201 ng/mL
IGF1 Z SCORE	0.13	NEG 2.0 - +2.0

	9/23/2019 1541	4/8/2019 1603	3/26/2018 1454	4/21/2017 0753
DIABETIC SCREENING...				
Glucose, Non-Fasting				
Hb A1C	*5.7 ** ▲			*4.8 **

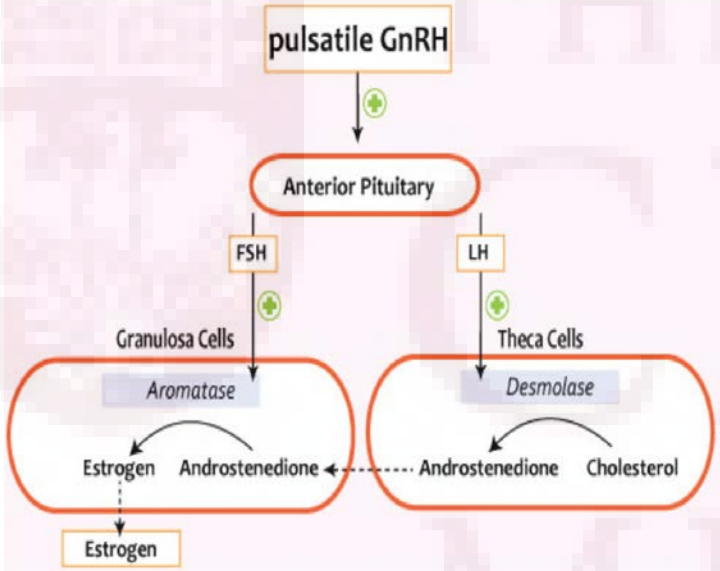
FSH 42.2 (20-135)

Imaging

- CT UPPER ABD AND PELVIS W 9/23/2019
- ADRENAL GLANDS: No significant abnormality noted., LYMPH NODES: No significant abnormality noted. PELVIS: Exam suboptimal due to beam hardening artifact from right hip prosthesis. UTERUS, ADNEXA: Status post hysterectomy. **IMPRESSION: Unremarkable study.**



Non tumorous (functional) hyperandrogenism	
Polycystic ovary syndrome	
Congenital adrenal hyperplasia	
Ovarian hyperthecosis	
Obesity	
States of insulin resistance	
Endocrinopathies	Cushing's syndrome
	Acromegaly
Iatrogenic	Testosterone/DHEA supplementation
	Antiepileptics (valproic acid and oxcarbazepine)
	Danazol
Tumorous hyperandrogenism	
Adrenal tumors	Androgen-secreting carcinomas
	Androgen-secreting adenomas
Ovarian tumors	Sertoli–Leydig cell tumors (androblastomas)
	Hilus cell tumors
	Granulosa theca cell tumors
	Metastatic neuroendocrine/ gastrointestinal tumors
	Cystadenomas

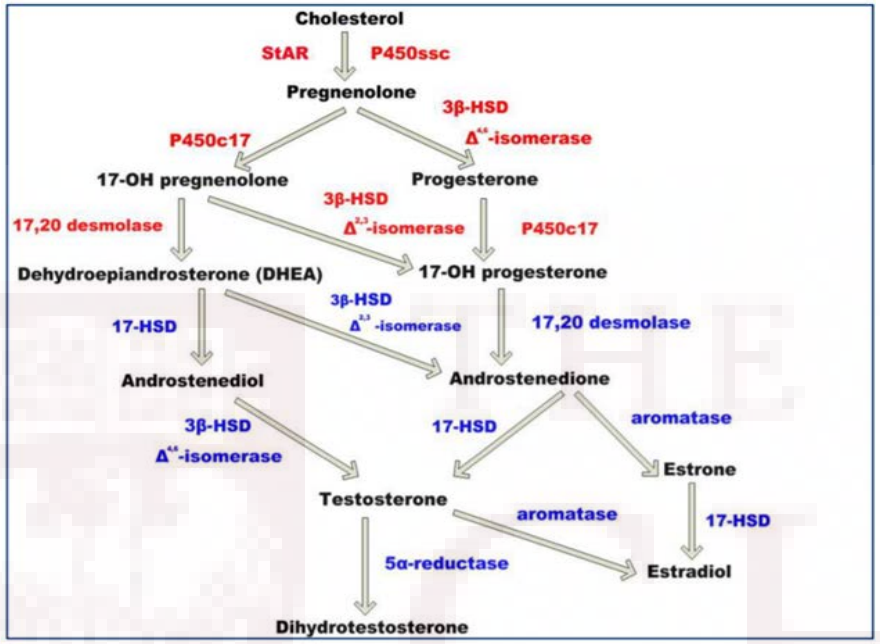


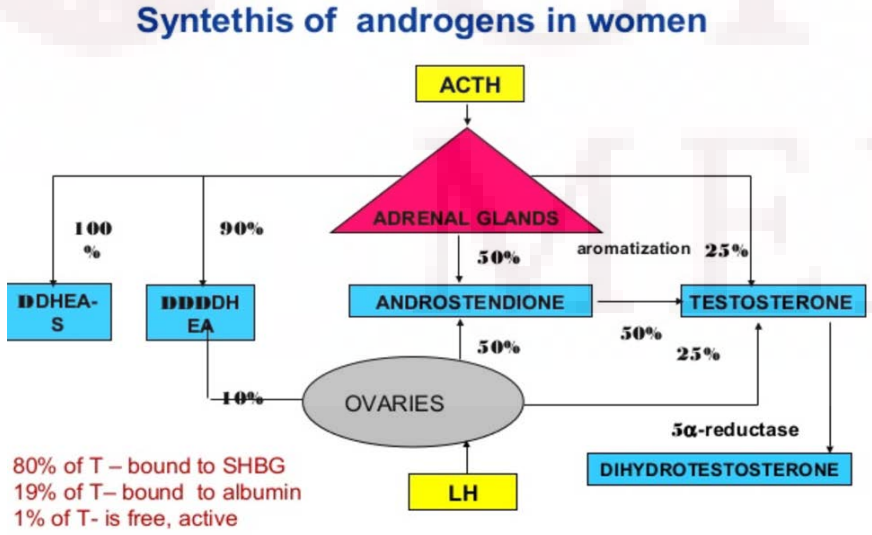
Is it physiologic/functional?

- The postmenopausal ovary remains hormonally active, secreting significant amounts of androgens and estrogens, many years after menopause [10]. Estrogen levels drop abruptly after menopause whereas androgen secretion gradually declines during the reproductive years. Subsequently, an imbalance among estrogens and androgens during menopause, amplified by a decrease in SHBG concentrations and may result in hyperandrogenic symptoms
- May be more pronounced in women with prior Dx of PCOS and CAH

Is it exogenous?

- Exogenous testosterone
- supplements
- Medications



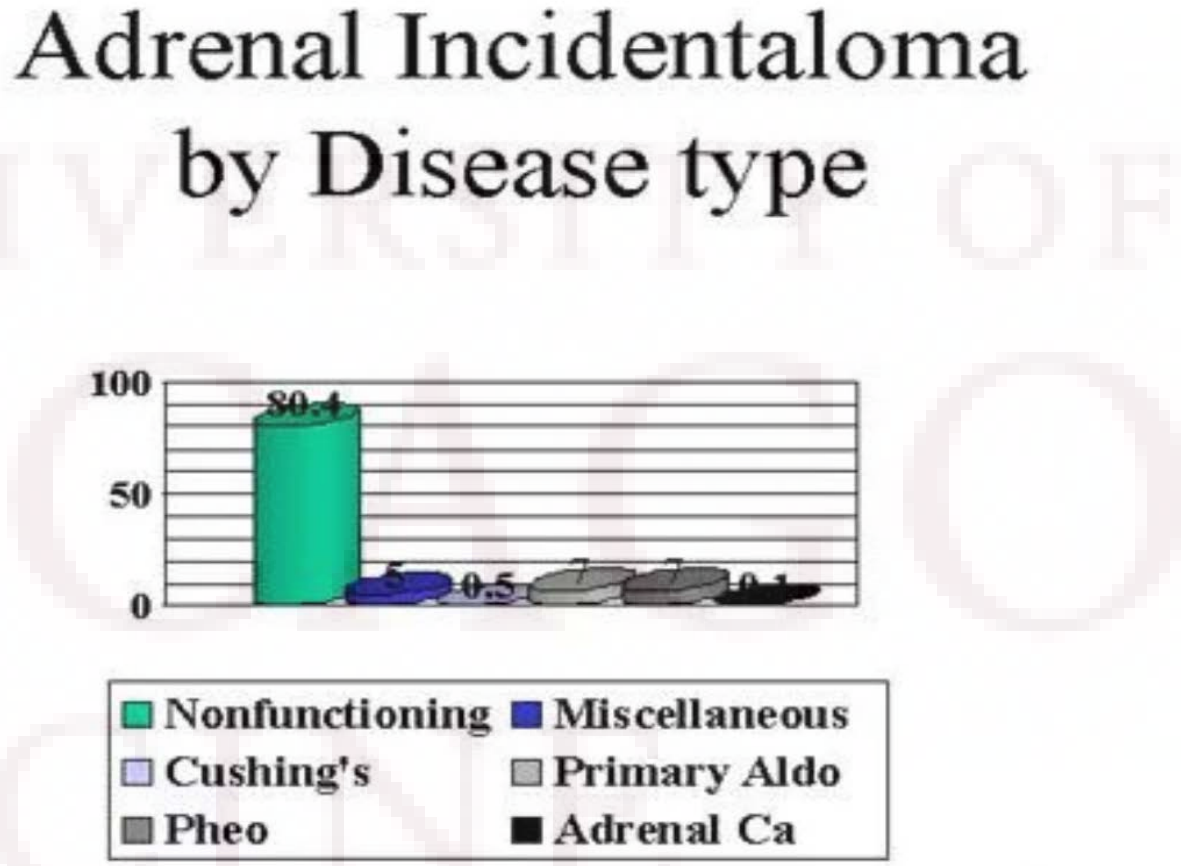


Is it adrenal?

- Cushing's syndrome (CS) may also be diagnosed after menopause and cause symptoms or signs of androgen excess. Hirsutism can be found in approximately 50% of patients with CS mainly attributed to adrenal androgen excess; endogenous hypercortisolism also correlates positively with free androgen levels probably due to SHBG reduction. In contrast to CS secondary to adrenal carcinomas, signs of hyperandrogenism are usually mild in women with the adrenocorticotropin- (ACTH-) dependent CD and are virtually absent in women with adrenal adenomas

Androgen secreting adrenal tumors

- Incidence ~ 1-2cases/million population per year, usually malignant
- Adrenal androgen-secreting neoplasms are usually large and aggressive carcinomas that present also with Cushing's syndrome (25%) and have a very rapid progression and almost invariably a fatal outcome
- The differentiation between adrenal adenomas and carcinomas depends not on histology but on the benign or malignant clinical outcome after successful surgery.
- adrenal tumors frequently present with increase DHEAS levels, however testosterone was shown be the most consistently elevated androgen
- probability of adrenal incidentaloma in patient over 70 yr of age reaches 7%



Is it ovarian?

Hyperthecosis ovary

- Hyperthecosis is a severe form of PCOS and results from an overproduction of androgens in the ovarian stromal cells. typically presents with slowly progressive acne and likely to be virilized.
- exact etiology is unclear thought to be related to elevated postmenopausal gonadotropin levels
- patients with hyperthecosis typically have normal serum dehydroepiandrosterone sulfate (DHEA sulfate) concentrations, testosterone >150 ng/dL and elevated gonadotropin levels
- Ultrasonography in women with hyperthecosis usually shows a bilateral increase in ovarian stroma and the ovaries appear more solid.
- characteristics of hyperthecosis include severe hyperandrogenism, insulin resistance (hiperinsulinism that further increase androgen production by binding to IGF1 receptors), hirsutism, and virilization
- Dx – histologic examination

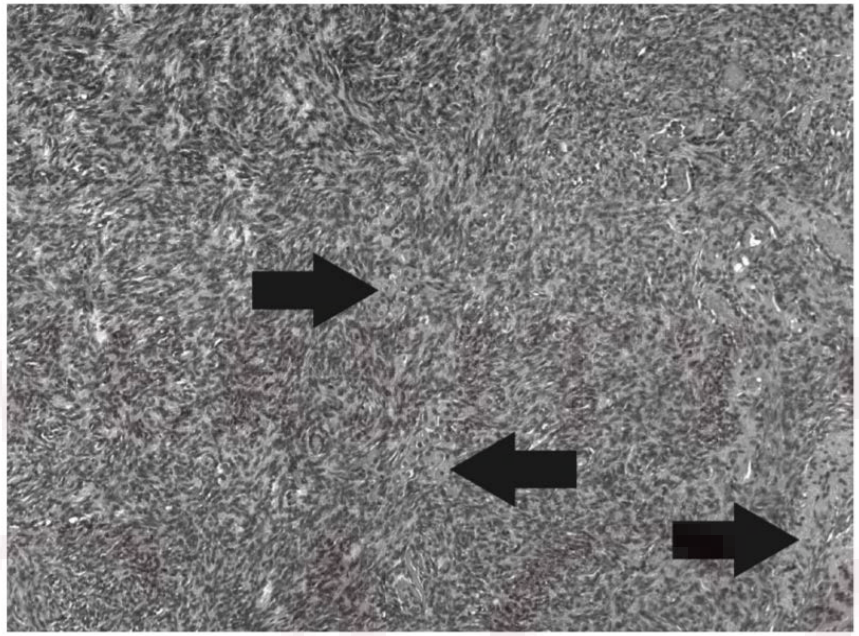
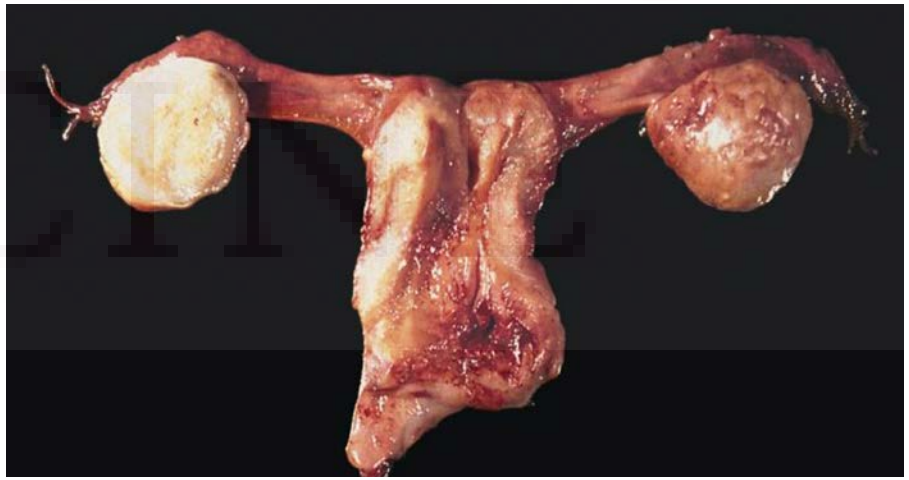


FIG. 2. Histological examination of the ovaries showing the nests of luteinized theca cells (*black arrows*) scattered throughout a hyperplastic ovarian stroma characteristic of ovarian hyperthecosis.



Is it ovarian?

- Sertoli-Leydig cell tumors (androblastoma) <1%, large at the time of presentation, ¼ presents at menopause
- granulosa-theca cell tumors (> estradiol, ~10% androgen secreting)
- hilus-cell tumors (more freq. in postmenopausal, small at the time of Dx, highly elevated testosterone levels);
- estradiol and testosterone, inhibin and anti-Mu¨llerian hormone can be used as specific tumor markers
- majority of ovarian androgen-secreting tumors is of relatively large size, ranging between 3 and 12 cm at diagnosis, and only a small minority may elude detection with current imaging modalities.
- Besides sex cord-derived tumors, androgen secretion may be the result of ovarian metastases from neuroendocrine tumors, other malignancies, and serous cystadenomas that are not known to be steroidogenic. In such cases, ectopic secretion of b-hCG has been speculated to stimulate the steroidogenic cells through a paracrine mechanism

Histologic type	Age at presentation (years)	Incidence (of all ovarian neoplasms, %)	Hormone secretion	Symptoms	Bilaterality	Malignant potential
Sertoli–Leydig cell tumors (androblastomas)	Range, 2–75	0.5	Androgens, rarely estrogens	Virilization in about one-third of cases	Uncommon (1–2%)	Low
Granulosa cell tumors	40–70	2–3	Estrogens, rarely androgens	Postmenopausal bleeding, mass, rarely virilization	About 5%	Low
Sertoli cell tumors	Range, 7–79	0.1	Androgens, rarely estrogens	Virilization in about 30% of patients	Rare (1–2%)	Low
Hilus cell tumors	Peak at 6th decade	0.02	Androgens	Hirsutism and virilization in 50–75% of cases	Rare	Very rare

Gonadotroph cell tumor

Cell type	Hormone expression	% Nonfunctional tumors
Null cell	None	17
Oncocytoma	None	6
Silent corticotroph	ACTH	8
Silent somatotroph	GH	3
Gonadotrophs	Intact LH/FSH or subunits	40-79

Classification of nonfunctional pituitary adenomas by cell of origin

Most hormonally silent tumors (NFPA), usually express gonadotropin subunits detectable by immunohistochemistry but not sufficient to elevate blood levels.

Most macro adenoma

Usually discovered because of space occupying defects, loss of vision, hypopit, hyperprolactinemia

Extremely rare

MANAGEMENT: surgery If threaten vision or macroadenoma. Although GnRH antagonists and somatostatin analogues modestly shrink tumor in some patients they are not sufficiently effective to be recommended as a therapy

Acromegaly

Acromegaly is a rare cause of hyperandrogenism in women, although hirsutism and less commonly acne can be found in up to 50% of the patients

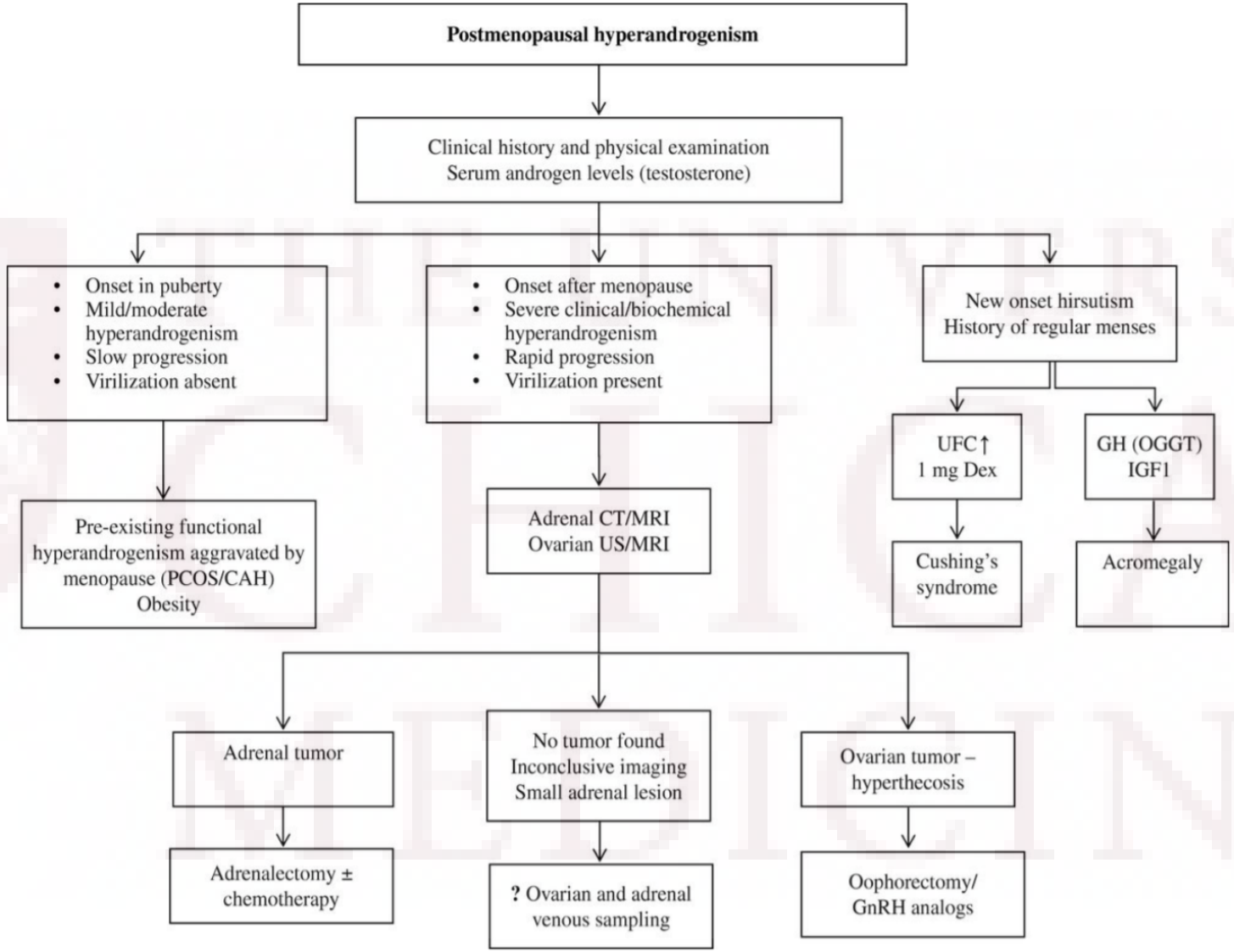
Growth hormone (GH) hypersecretion induces a state of ovarian hyperandrogenism that along with the increased insulin-like growth factor 1 levels and concomitant hyperinsulinemia stimulate ovarian testosterone production. In addition, GH levels correlate negatively with SHBG levels, contributing to elevated free androgen levels

Differential diagnosis of clinical hyperandrogenism

Diagnosis	Frequency (percent)	Age of onset years	Time of onset to presentation	Menstrual disturbance	Virilization
PCOS and related disorders	>95	15 to 25	Years	+/-	Rare
CAH	1 to 2	Congenital	Birth/adolescence/adulthood	+	+/-
Adrenal tumor	<1	Any time	Weeks-months	+	+
Ovarian tumor	<1	Any time	Weeks-months	+	+
Cushing's syndrome	<1	Any time	Months-years	+	+/-
Hyperthecosis ovary	<1	Pre- to post-menopause	Months-years	+	+

PCOS: polycystic ovary syndrome; CAH: congenital adrenal hyperplasia; (+): present; (-): absent; (+/-): present or absent.

From: Dennedy MC, Smith D, O'Shea D, McKenna TJ. Investigation of patients with atypical or severe hyperandrogenaemia including androgen-secreting ovarian teratoma. Eur J Endocrinol 2010; 162:213. Copyright © Society of the European Journal of Endocrinology 2010. Reproduced by permission.



European J of endocrinology 2015

Lab evaluation

- Pit. axis eval (LH, FSH, alpha-subunit, PRL, T4, T3, TSH, cortisol, IGF1, DHEA and DHEAS
- cosyntropin stim (with venous sampling)
- Low dose dexamethasone suppression: sensitivity of 100% and a specificity of 88%
- GnRH suppression
- TRH stimulation (most NFTs are capable of synthesizing gonadotropin hormones and subunits (beta-FSH, beta-LH). Most patients in our study responded by either FSH, LH or alpha-SU secretion after TRH, independent of basal hormone levels. Furthermore, recent studies show that by measurement of TRH stimulated beta-FSH and beta-LH one might further improve the diagnostic tools. Gonadotropin response and possibly alpha-SU to TRH are also found in some patients with acromegaly. This could be a marker of a plurihormonal pituitary tumor)

imaging

- CT/MRI adrenal
- US ovaries (transvaginal)
- If no tumor detected imaging of ovaries and adrenals after IV radiolabeled iodomethylnorcholesterol (NP-59) (detects active steroid producing tumors)
- **Selective ovarian or adrenal vein catheterization and sampling** may be considered before surgical exploration, but simultaneous catheterization of all adrenal and ovarian veins is difficult, with success rates as low as 26 – 45%. procedure consists of introducing a femoral catheter to reach both the adrenal and ovarian veins. Adrenal and ovarian venous sampling with peripheral vein control is performed simultaneously, androgen concentrations (usually testosterone) are measured, and the adrenal or ovarian/peripheral gradient is calculated. In the adrenal sample, cortisol is also measured to ensure that the catheter is properly placed. Unilateral adrenal and ovarian lesions are associated with an ipsilateral gradient and different threshold values have been proposed to discriminate tumoral from non-tumoral causes. Gradients >4.51 nmol/L have a reported sensitivity and specificity of 94% and 78%, respectively. Venous sampling has also been reported to predict the correct localization of the lesion in 66% of cases. The limitations of lesion localization using venous sampling include the technical difficulty associated with the accurate catheterization of 4 veins, with a 4 vein catheterization success rate of 27 to 45%.
- WBPET (9)

Treatment options

	Treatment
Non tumorous etiology	
Functional hyperandrogenism (PCOS, NCAH, and obesity)	Cyproterone acetate Spironolactone/flutamide Insulin sensitizers (metformin) Local therapies (hirsutism) Diet and exercise
Ovarian hyperthecosis	Surgical resection/GNRH analogs
Iatrogenic	Discontinuation of drugs/ supplements
Endocrinopathies	
Cushing's syndrome	Surgical resection/adrenolytics
Acromegaly	Surgical resection/Somatostatin analogs/pegvisomant
Tumorous etiology	
Adrenal tumors	Surgical resection (stage I/II) Adjuvant therapy – mitotane (stage III/IV)
Ovarian tumors	Oophorectomy GNRH analogs

PCOS, polycystic ovary syndrome; NCAH, non-classic adrenal hyperplasia.

- Long-term GnRH agonist treatment is an acceptable choice for treatment of postmenopausal hyperandrogenism in patients where ovarian origin of androgen excess is ascertained, and especially in those patients who have an increased risk for surgery due to comorbidities or who are unwilling to undergo bilateral oophorectomy.

Back to our patient

Right Ovary	Visualized. Outline: smooth. Size 18 mm x 15 mm x 10 mm. Vol 1.5 cm^3
Left Ovary	Visualized. Size 17 mm x 13 mm x 13 mm. Vol 1.5 cm^3
Cyst(s)	Size 12 mm x 10 mm x 13 mm. Mean 11.7 mm. Vol 0.817 cm^3. unilocular cyst, smooth internal wall, cystic contents with 'ground glass' appearance, acoustic shadows not present, color score 2 (minimal color). Presumed endometrioma vs. unknown pathology
Cul de Sac	Visualized. No free fluid visualized
Impression	Ms. DUPREE is referred for an ultrasound at the Center for Advanced Care for high serum testosterone, hirsutism. History of hysterectomy in 1998. Patient states history of left ovarian cyst.

Multiple transabdominal and transvaginal images were taken to evaluate the pelvis.
Transvaginal ultrasound imaging is limited due to ovarian mass, therefore, transabdominal images were obtained to better visualize the entire pelvis.
Uterus is surgically absent.
Vaginal cuff appears unremarkable.
Right ovary appears within normal limits.
Left ovary is seen with a 12 x 10 x 13 mm unilocular cyst as described above.
No free fluid is visualized in the cul- de- sac.
Previous ultrasound on 12/10/2007.

Take home points

- Careful history taking is important
- Laboratory investigation can guide in a right direction, but none are 100% reliable
- Positive imaging findings must always be interpreted carefully while taking into account the clinical context of the patient
- After menopause, ovarian causes of hirsutism and virilization are more frequent compared with adrenal disorders and include androgen secreting neoplasms and benign disorders such as ovarian stromal hyperplasia and hyperthecosis

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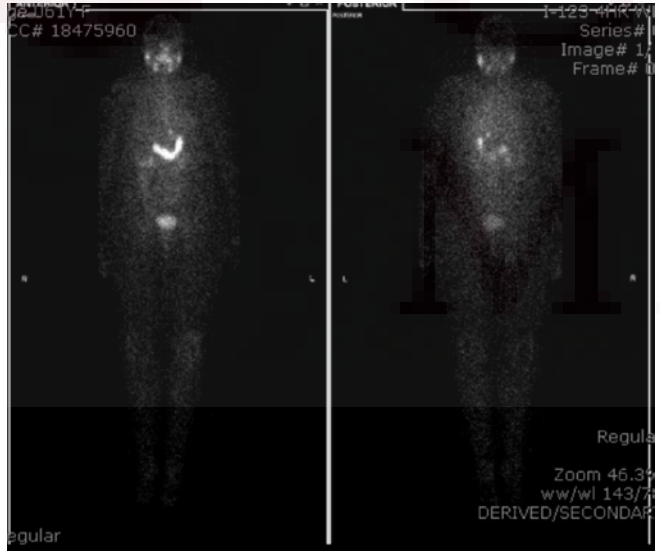
	6/5/2017 1701	10/9/2017 1343	4/10/2018 1217	4/18/2018 0839	5/11/2018 1423	7/18/2018 1127
THYROID FUNCTION						
ALPHA-SUBUNIT						
Thyroxine, Free	*1.24 **	*1.38 **	*2.20 **	*0.63 **	*1.05 **	*1.37 **
Reverse Triiodothy...					*201 **	
Thyroglobulin Ab			*<0.4*			
Thyroglobulin (Thy...			*<1 **			
THYROID STIMULATIN...						
Thyroid Perox. Ab			*0.6*	*0.5 ** c		
Thyrotropin	*0.66*	*0.19*	*0.01*		*1.28*	*0.73*
Triiodothyronine			*246*	*79*	*96*	

NM THYROID IMG SNG/MLT UPTKS QNT MSRMNTS, 4/17/2018 : no functioning thyroid tissue



- **US thyroid 4/16/2019**

Small relatively echogenic appearing soft tissue foci in the thyroid bed bilaterally, suspected to be residual thyroid tissue. Correlation with nuclear medicine study and surgical history recommended

Postmenopausal hyperandrogenism

- a state of relative or absolute androgen excess originating from either the adrenals and/or the ovaries, clinically manifested as the appearance and/or increase in terminal hair growth or the development of symptoms/signs of virilization