THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

“51 year old woman with hirsutism”

Dr. Darji does not have any relevant financial relationships with any commercial interests.

51 year old woman with hirsutism

Monika Darji, PGY6

January 28, 2021

Objectives

- Discuss causes of hirsutism
- Discuss evaluation and management of postmenopausal hyperandrogenism

51 year old woman

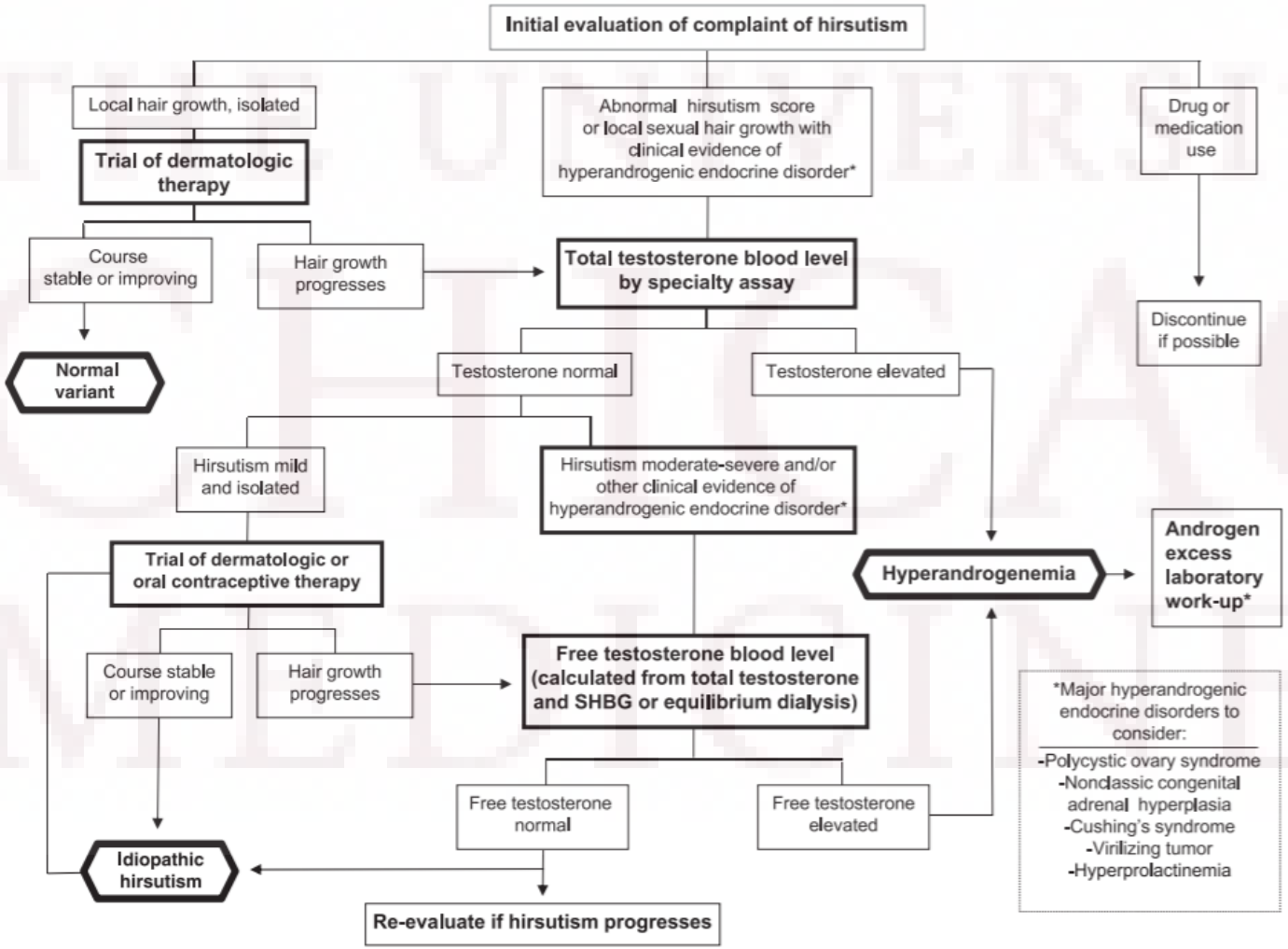
- Presented to OSH Family Medicine in 8/2018 with chief complaint of hirsutism
  - Menopause at 44 years old
  - Worsening dark hair growth on face for last 5 years
  - Menses regular prior to menopause
  - No history of PCOS
  - Family history – father had pheochromocytoma

Medical History

- Past Medical History
  - HTN
  - Depression
  - OSA
  - Obesity
  - Multinodular goiter
- Past Surgical History
  - Left shoulder and ankle surgery
- Social History
  - Smokes 0.5 ppd x 30 years
  - Denies alcohol, illicit drugs
- Family History
  - Mother – breast cancer
  - Father – pheochromocytoma
- Allergies: NKDA
- Medications
  - Paroxetine 40 mg daily
  - Diltiazem 180 mg

What tests would you order?

Hirsutism workup



Martin et al Guidelines on Hirsutism

J Clin Endocrinol Metab, April 2018, 103(4):1233–1257

Initial Labs

A1c 6.1%
TSH 1.1

AM cortisol (9am) – 9.9 ug/dL
DHEA-S – 62 ug/dL (41.2 - 243.7 ug/dL)
Total testosterone – 355 ng/dL (7 – 40 ng/dL)
Free testosterone – 229 ng/dL (1.1 -14.3 ng/dL)

Next steps?

Follow up

- Patient was started on spironolactone 50 mg and referred to OSH Endocrinology
- Endocrinology arranged for CT abdomen imaging
- Follow up visit with PCP in 9/2018
  - No change in hirsutism
  - Spironolactone dose increased 50 mg -> 100 mg daily
  - Started on metformin 500 mg

CT Abdomen

11/2018

CLINICAL INDICATION: 51 years-old Female with elevated testosterone level.

COMPARISON: None.

TECHNIQUE: CT abdomen and pelvis with intravenous contrast. Radiation dose reduction protocol.

FINDINGS:

Adrenals:

Right: There is a little low density lateral limb adrenal nodule measuring 3.0 cm x 2.0 cm. On the precontrast images, this demonstrates a Hounsfield unit of 3.2, compatible with the adrenal adenoma. No associated enhancement is noted on the arterial phase images or on the adrenal washout images on the 15 minute delayed image.
Left: There are numerous low-density adrenal nodules. There is suggestion of a septation and given the presence of the septation, contrast was administered. A medial limb nodule measures up to 3.7 x 2.7 cm. This demonstrates 10 Hounsfield units. A lateral limb adrenal nodule measures 3.7 x 2.7 cm. The lateral limb nodule demonstrates Hounsfield unit of 1 on precontrast images compatible with adrenal adenomas. There is moderate enhancement noted with the lateral limb adrenal nodule on the arterial phase image, which measures up to 15 on the delayed image, the lateral limb nodule demonstrates Hounsfield units of 30.

In the remainder of the exam, there are subcentimeter nonenhancing hepatic lesions compatible with cysts, largest measuring up to 1.0 cm. Mild diffuse hepatic steatosis is present. No calcified gallstones or biliary ductal dilatation The spleen demonstrates punctate splenic hypodensities which are nonspecific. The pancreas is within normal limits.

The visualized portion of the bowel is grossly within normal limits. No bowel obstruction.

The kidneys demonstrate subcentimeter renal hypodensities which are too small to characterize by any modality but statistically suggestive of cysts. No abdominal lymphadenopathy or ascites.

The visualized osseous structures demonstrate no significant degenerative arthropathy.

IMPRESSION:

1. There are bilateral adrenal nodules which demonstrate no significant enhancement and compatible with adenomas. Given the presence of elevated testosterone, these may represent functional adenoma.
2. Hepatic steatosis with suggestion of hepatic cyst.
3. Too small to characterize renal hypodensities bilaterally

Next steps?

Adrenal incidentaloma

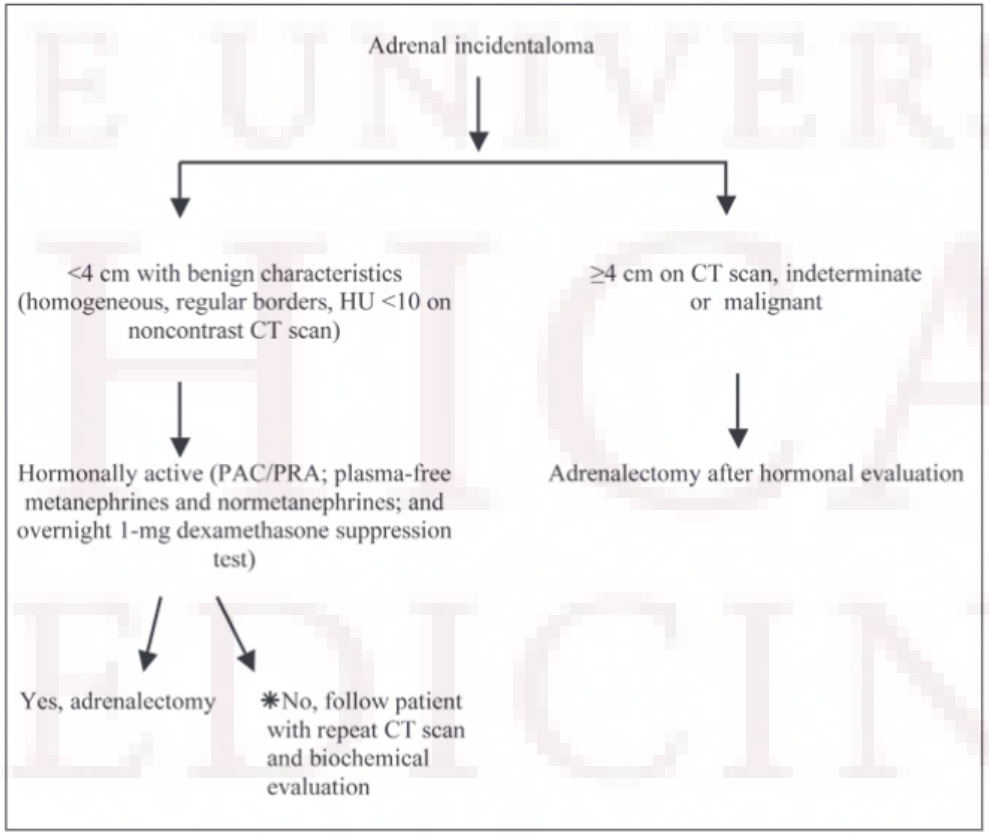


Fig. 1. Algorithm for the evaluation and management of an adrenal incidentaloma. * = Reimage in 3 to 6 months and annually for 1 to 2 years; repeat functional studies annually for 5 years. If mass grows more than 1 cm or becomes hormonally active, then adrenalectomy is recommended. *CT* = computed tomographic; *HU* = Hounsfield units; *PAC* = plasma aldosterone concentration; *PRA* = plasma renin activity.

Zeiger et al. Endocrine Practice (2009).

Further workup by OSH Endo

- 24 hour urine testing:
  - Free cortisol – 46 (0 - 50 ug/24 h)
  - Epinephrine – 2 (0 - 20 ug/24 h)
  - Norepinephrine – 48 (0 - 135 ug/24 h)
  - Dopamine – 170 (0 - 510 ug/24 h)
  - Normetanephrine – 695 (82 - 500 ug/24 h)
  - Metanephrine – 98 (45 - 290 ug/24 h)
- Plasma normetanephrine – 136 (0 - 145 pg/mL)
- Plasma metanephrine – 20 (0 - 62 pg/mL)
- Plasma aldosterone – 26 (0.0 - 30.0 ng/dL)
- Plasma renin activity – 4.8 (0.167 - 5.380 ng/mL/h)

Thoughts?

Referred to Endocrine Surgery at UCM

- Seen by endocrine surgery in 3/2019 for surgical evaluation
  - Planned to monitor adrenal nodules – since they did not meet size criteria and were thought to be nonfunctional
  - Adrenal vein sampling for testosterone levels
  - Repeat CT scan in 6 months

Adrenal vein sampling (7/2019)

	Total Testosterone (ng/dL)	Cortisol (ug/100ml)
Right adrenal vein	260	84.6
Right adrenal vein repeat 1	543	610
Right adrenal vein repeat 2	567	680.9
Left adrenal vein	994	647.9
Left adrenal vein repeat 1	982	589.1
Femoral vein	222	59.6
Femoral vein repeat 1	230	64.9

Combined adrenal and ovarian venous sampling

- Considered in postmenopausal patients with tumor range testosterone levels with small adrenal adenoma and normal imaging of the ovaries or in premenopausal women interested in future fertility
- Technically difficult procedure
- Successful cannulation rate of both adrenal veins and both ovarian veins ranges from 27 to 45%
- No consensus regarding the testosterone gradient that localizes the androgen source

Further workup

- 6 month follow up CT abdomen w/o contrast in 6/2019
  - “Redemonstration of bilateral low-density adrenal gland nodules measuring up to 2.8 cm on the right and 4.3 cm on the left with attenuation characteristics most compatible with lipid rich adenomas”
- Repeat CT Abdomen with and without contrast in 6/2020
  - Right adrenal adenoma 3.4 cm x 2.5 cm
  - Left adrenal adenoma 4.7 x 3.6 cm
  - No enhancement and are consistent with lipid rich adenomas
- 8/2020 labs:
  - Total testosterone – 168 ng/dL (7 – 40 ng/dL)
  - Free testosterone – 130 ng/dL (1.1 -14.3 ng/dL)
  - AM cortisol (8am) after DST – 10 ug/dL
- 8/2020 – Endocrine surgery appointment
  - Ordered MN salivary cortisol and ACTH
  - Endocrinology clinic referral

Thoughts?

Initial endocrinology clinic visit

- History:
  - No acne, history of acne at a young age
  - Mild hair thinning from front of scalp recently
  - Gained 100 pounds over the past two years
  - Easy bruising
  - Easily fatigued
  - No muscle weakness
  - Feels her face is fuller

- Exam:
  - BP 132/80
  - Central obesity
  - No dorsocervical fat pad
  - Deep voice
  - Terminal facial hair
  - Striae on abdomen
  - 5/5 Muscle strength

Further workup

- FSH 13.7 (20-135 mIU/mL)
- Estradiol 27.6 pg/mL (2 – 21 pg/mL)
- DHEA-S – 70.6 ug/dL (41.2 - 243.7 ug/dL)
- Total testosterone – 129 ng/dL (7 – 40 ng/dL)
- Free testosterone – 60 ng/dL (1.1 - 14.3 ng/dL)
- Te Binding globulin 11 nmol/L
- ACTH - < 3 pg/mL (<52 pg/mL)
- MN saliva cortisol – 146 ng/dL (<100 ng/dL)
- AM cortisol (8:30 am) after DST – 8.5 ug/dL
  - Dexamethasone level 619 ng/dL

Thoughts?

Establishing Cushing's diagnosis

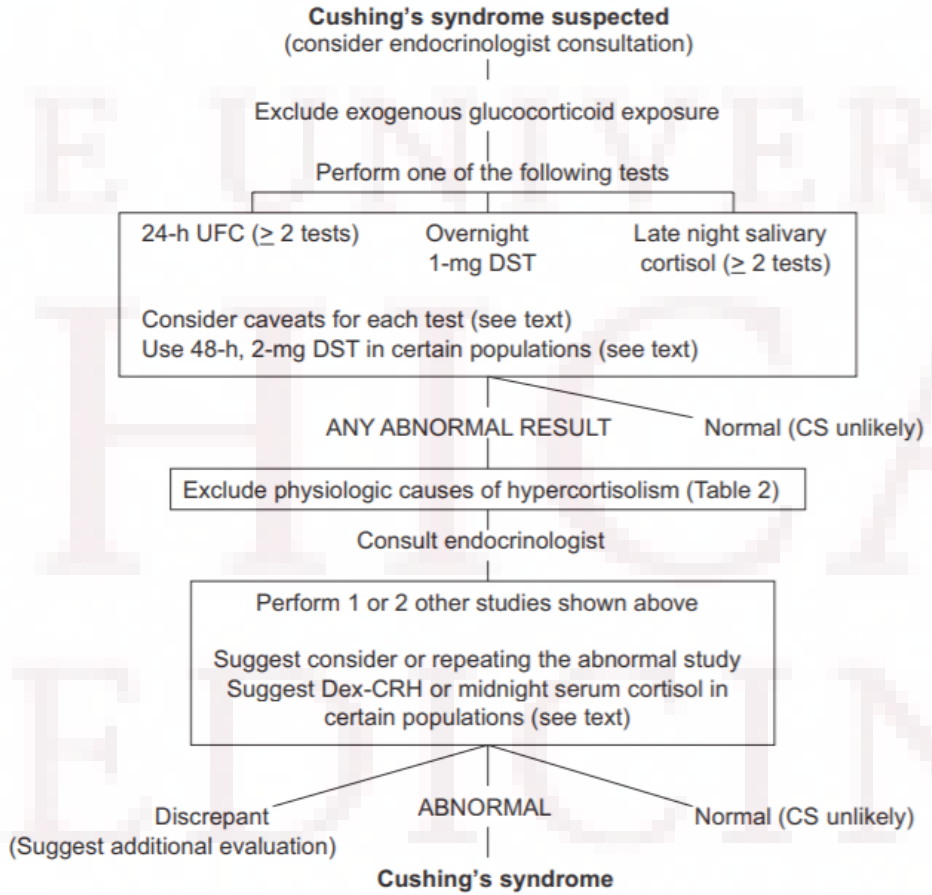
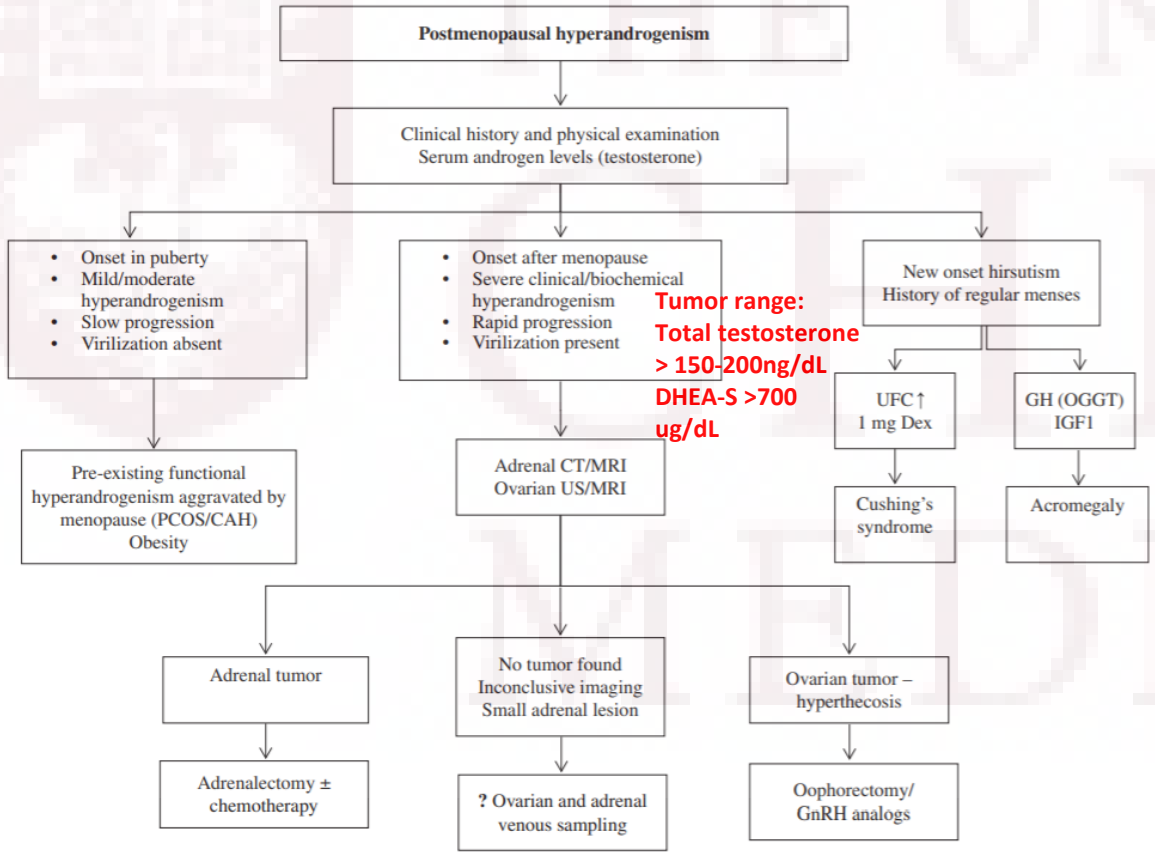
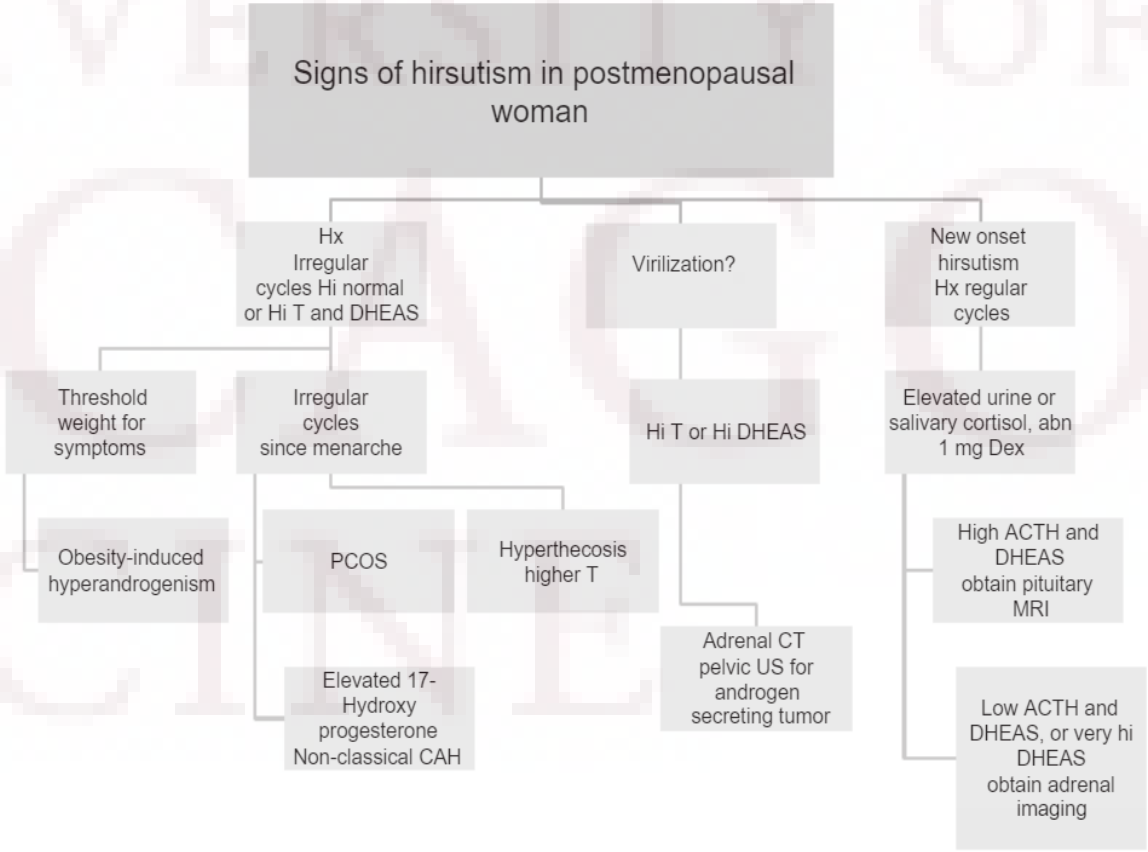


FIG. 1. Algorithm for testing patients suspected of having Cushing's syndrome (CS). All statements are recommendations except for those prefaced by suggest. Diagnostic criteria that suggest Cushing's syndrome are UFC greater than the normal range for the assay, serum cortisol greater than 1.8 μg/dl (50 nmol/liter) after 1 mg dexamethasone (1-mg DST), and late-night salivary cortisol greater than 145 ng/dl (4 nmol/liter).

Post menopausal hyperandrogenism workup



Markopoulos, et al. European Journal of Endocrinology (2015)



Rothman et al. Clinical Endocrinology (2011)

Post menopausal hyperandrogenism workup

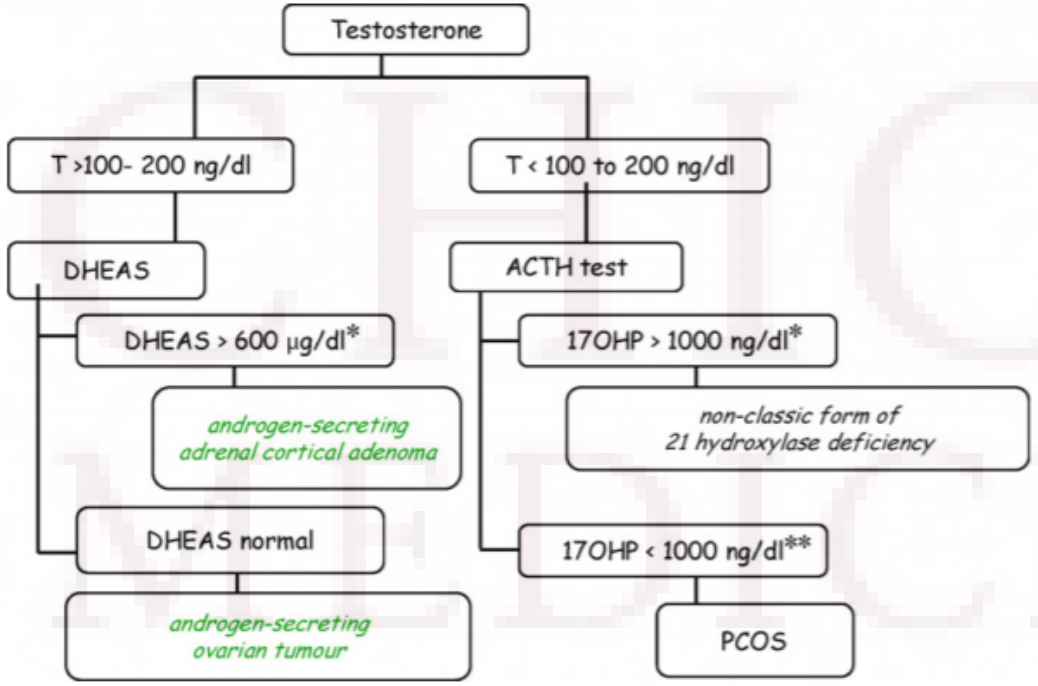


Fig. 3. Decision tree for total testosterone tumoural elevation: twice the upper limit of normal, or greater than 100 ng/dl (3.5 nmol) (assay with extraction) or 200 ng/dl (7.0 nmol) (direct assay). * 16000 nmol/l. ** 30.3 nmol/l.

Pugeat et al. Annales d'Endocrinologie. 2010.

- DHEA-S is primarily of corticoadrenal origin
- DHEAS level of over 600g/dl indicates a diagnosis of androgen-secreting adrenal cortical adenoma (often associated with hypercortisolemia)
- Abdominal imaging is the next step

Post menopausal hyperandrogenism

Table 1 Causes of hyperandrogenism in women after menopause.

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

Markopoulos, et al. European Journal of Endocrinology. 2015

Next steps

- High suspicion for ovarian tumor leading to tumor range testosterone elevation
  - Pelvic ultrasound to evaluate for ovarian mass
- Bilateral adrenal masses with evidence of hypercortisolemia
  - Nonsuppressed cortisol of 8 post overnight DST
  - Elevated midnight saliva cortisol
  - ACTH and DHEAS are low as suspected with adrenal source
  - PET-CT to better determine functionality of the adrenal lesions and also look for ovarian abnormality

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IMAGE IN ENDOCRINOLOGY: Testosterone-Secreting Ovarian Tumor Localized with (Fluorine-18)-2-Deoxyglucose Positron Emission Tomography

Cecilia Mattsson, C. Robert Stanhope, Susan Sam, and William F. Young, Jr.

Department of Public Health and Clinical Medicine, Umeå University Hospital (C.M.), S-901 85 Umeå, Sweden; Division of Endocrinology, Metabolism, and Molecular Medicine, Northwestern University (S.S.), Chicago, Illinois 60611-3008; and Department of Obstetrics and Gynecology (C.R.S.) and Division of Endocrinology, Diabetes, Metabolism, and Nutrition (W.F.Y.), Mayo Clinic College of Medicine, Rochester, Minnesota 55905

CASE REPORT

Diagnosis and Localization of Testosterone-Producing Ovarian Tumors: Imaging or Biochemical Evaluation

Peng-Hui Wang, M.D.,*[,1] Hsiang-Tai Chao, M.D., Ph.D.,* Ren-Shyan Liu, M.D.,† Yi-Hung Cho, M.D.,‡ Heung-Tat Ng, M.D.,* and Chiou-Chung Yuan, M.D.*

**Departments of Obstetrics and Gynecology, †Nuclear Medicine, and ‡Radiology, Taipei Veterans General Hospital, National Yang-Ming University, Taipei, Taiwan*

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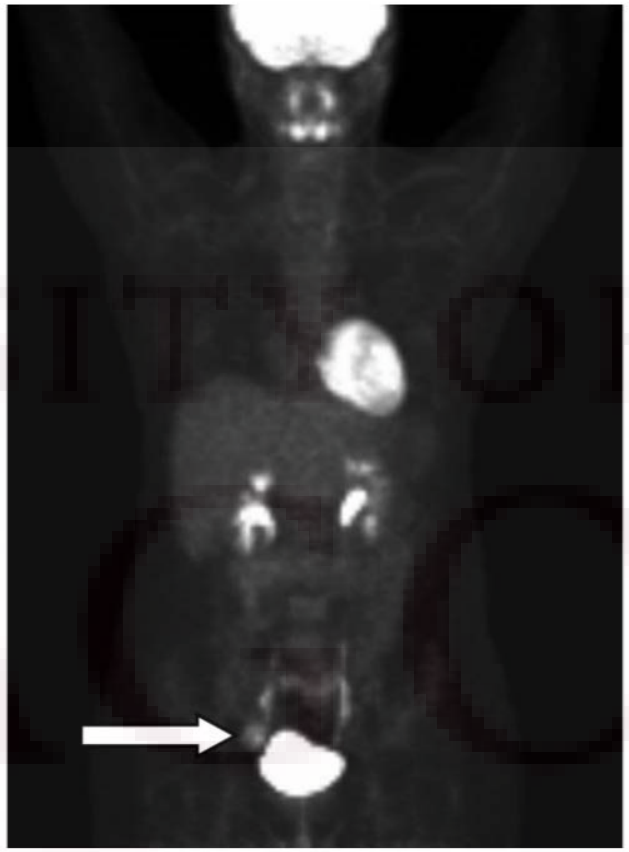


FIG. 2. FDG-PET scan showing increased uptake in right ovary (*arrow*).

- Case reports suggesting FDG-PET can be used in the localization of T-secreting ovarian neoplasms when CT, US, and venous sampling studies are inconclusive

Pelvic ultrasound 9/2020 - Ovaries are normal in size and appearance.

EXAM(S): PET SKULL BASE TO MID THIGH, INTL STAGE 10/02/2020 6:05 PM

COMPARISON: No previous PET here. Abdominal CT, from outside hospital on 6/26/2020

FINDINGS: Today's CT portion grossly demonstrates bilateral adrenal masses. The right adrenal mass, measuring 3.5 cm in diameter, demonstrates uniform low-attenuation with CT Hounsfield unit of -11. The left adrenal mass, measuring 5.7 cm in diameter, is lobulated with heterogeneous attenuation. The right Linear densities is seen in the right middle lobe. An exophytic nodule is seen in the uterus, which is most likely due to uterine fibroid.

Today's PET examination demonstrates intense focus of activity in the right thyroid gland with SUV max of 40.5. There is increased activity in the left adrenal lobulated the mass with SUV max of 6.0. There is a mildly increased metabolic activity in the right adrenal mass with SUV max of 2.7.

Focal skin activity in the right anterior pelvic wall is most likely due to inflammatory change.

FDG uptake in the remaining portion of the body is physiological.

IMPRESSION:

1.Hypermetabolic left thyroid nodule, which can be due to thyroid cancer. Suggest further evaluation with ultrasonography and biopsy.
2. Lobulated mass with heterogeneous attenuation and increased metabolic activity in the left adrenal gland, which can be due to adenoma or carcinoma.
3. Right adrenal mass with mild FDG uptake and hypoattenuation is most likely due to benign adrenal adenoma.

ADDENDUM:
PLEASE NOTE: THIS REPORT HAS BEEN ADDENDED AND SHOULD BE READ CAREFULLY FOR MODIFICATIONS AND/OR ADDITIONS.

On noncontrast nondiagnostic CT there is a soft tissue density in the left pelvis contiguous with uterus. On the PET study the soft tissue density has no increased metabolic activity. This finding could be due to left adnexal mass or pedunculated uterine fibroid.

Assessment

- Tumor range elevation of testosterone
- Evidence for Cushing syndrome
  - PET scan shows significant increase activity in the left adrenal gland compared to right -> source is likely left adrenal gland which is larger
  - Plan is for left sided adrenalectomy
- The ovaries appear normal on the pelvic US. On PET, there is a soft tissue density on the left adnexa
  - Plan is for contrast CT of pelvis to ensure no ovarian mass

CT abdomen and pelvis

EXAM(S): CT UPPER ABD AND PELVIS W 10/16/2020 11:35 AM

ADRENAL GLANDS: There is a right adrenal mass measuring 3.2 x 3.3 cm image #32, series #301 which is slightly increased in size compared to CT dated 11/13/2018. This lesion was measuring 2.9 x 2.5 cm on image #27, series #9 on that study. Same adrenal lesion has not significantly changed compared to CT from 6/26/2020.

There is a multilobulated left adrenal mass. Superior component of this mass now measures 4.8 x 3.6 cm image #32, series #301. This is slightly increased in size compared to CT from 11/2018 weight was measuring 4.3 x 3.6 cm. However this has not significantly changed compared to previous CT from 6/2020.

UTERUS, ADNEXA: There is a mass with possible enhancing components in the right adnexa measuring 3.9 x 3.1 cm image #106, series #301. This corresponds to the right ovarian mass which is FDG avid on on the PET/CT. CT of the pelvis is not included on the previous CTs, therefore, this lesion cannot be compared to the previous CTs.

IMPRESSION: Fatty infiltration of the liver and stable benign-appearing liver lesions.

Bilateral large adrenal masses which are slightly increased in size compared to 2018 but stable compared to the CT from June 2020.

Right ovarian mass with possible enhancing component. An ovarian malignancy cannot be excluded. Transvaginal ultrasound and/or MRI of the pelvis may be helpful for further evaluation.

OB/GYN follow up

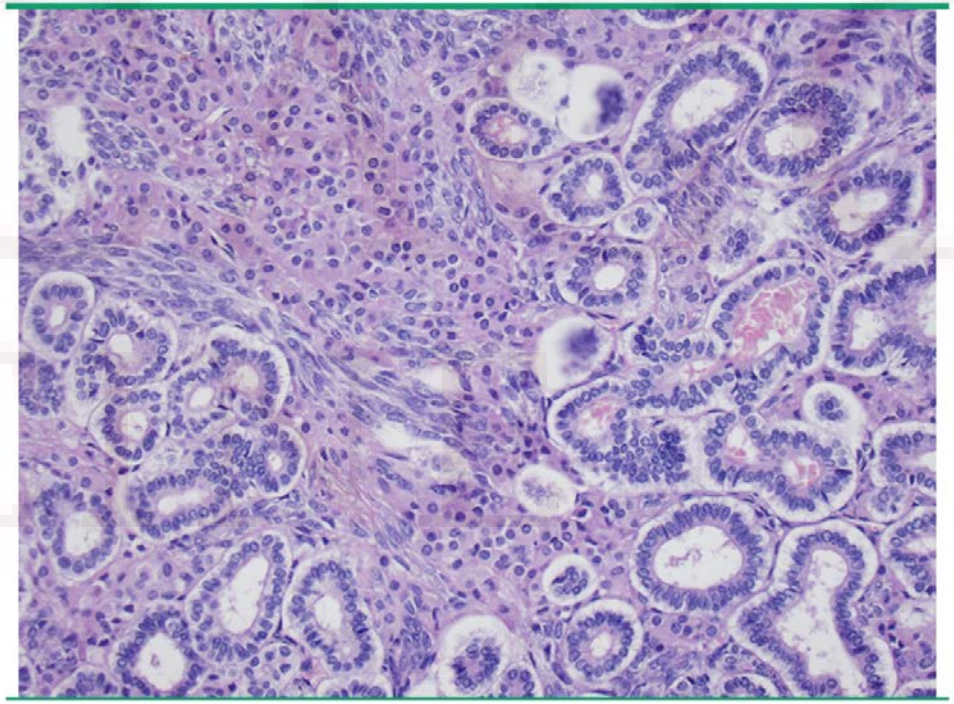
- 10/2020 appointment for adnexal mass
  - Concern for testosterone producing tumor like sex cord stromal tumor
  - Plan for surgical management with TAH/BSO
- 11/6/20 - Total laparoscopic hysterectomy with bilateral salpingo-oophorectomy and omentectomy

Sertoli Leydig tumor

- Path: Stage IA well differentiated Sertoli Leydig, no high risk features
- Plan: Recommended surveillance

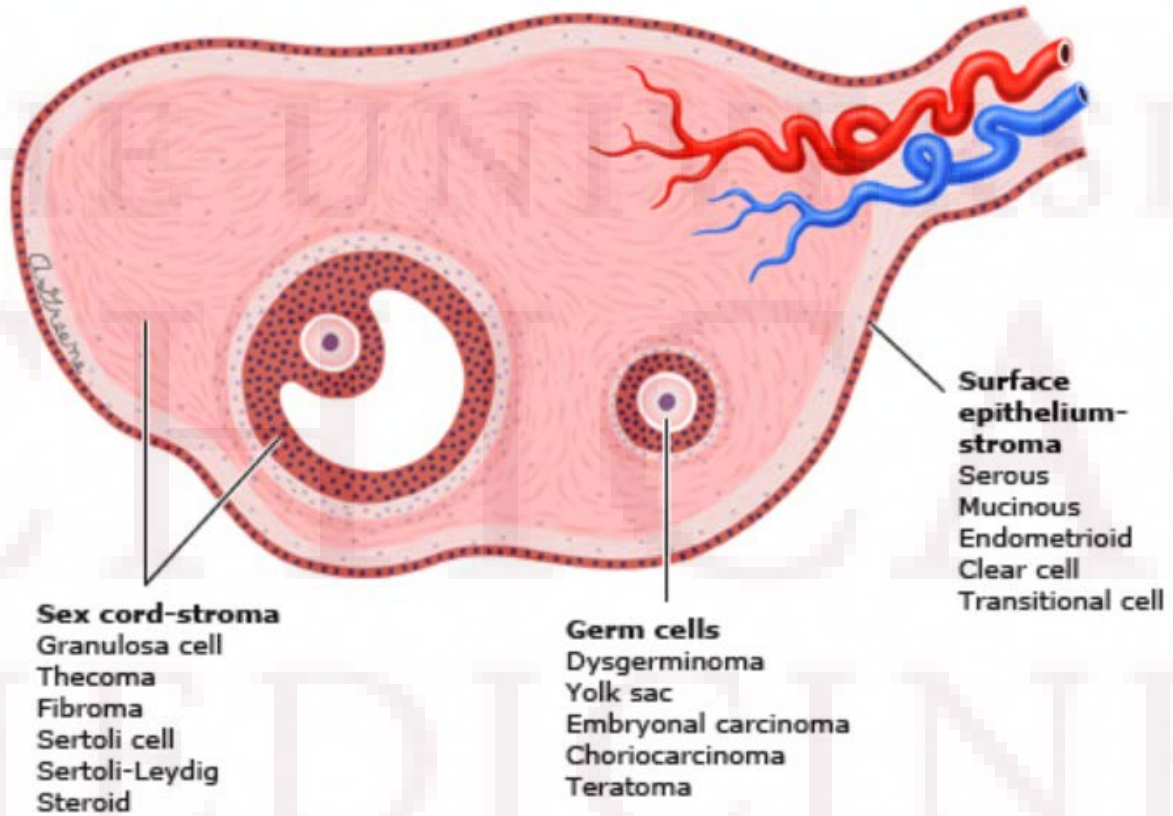
FINAL PATHOLOGIC DIAGNOSIS
A. Uterus, cervix, fallopian tubes and ovaries; hysterectomy and bilateral salpingo-oophorectomy:
- Right ovary with well-differentiated Sertoli-Leydig cell tumor (2.9 cm); see comment and synoptic report.
- Ovaries with stromal hyperthecosis.
- Inflamed cervix with squamous metaplasia.
- Inactive endometrium.
- Leiomyomas.
- Fallopian tubes without diagnostic abnormality.

Sertoli-Leydig cell tumor



Well-differentiated Sertoli-Leydig cell tumor.

Origins of ovarian tumors



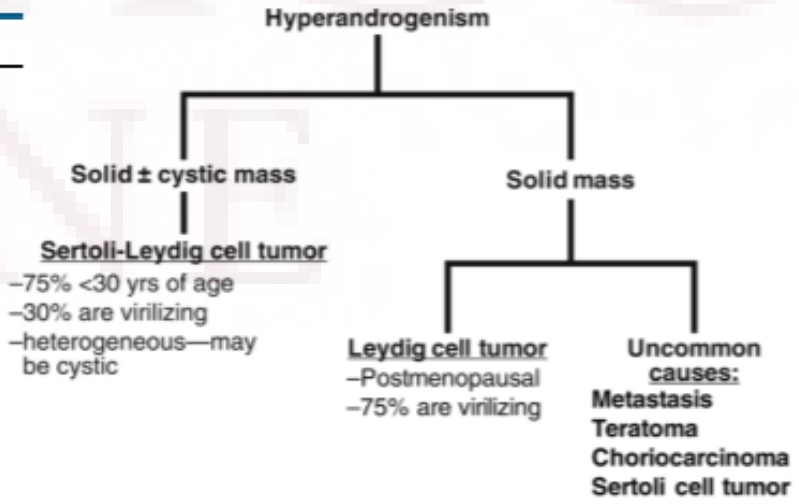
Many epithelial ovarian carcinomas, such as high-grade serous carcinomas, originate in the fallopian tube epithelium.

Androgen secreting ovarian tumors

Table 2 Ovarian androgen-secreting tumors in postmenopausal women.

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

Markopoulos, et al. European Journal of Endocrinology. 2015



Subsequent labs

- Post TAH-BSO surgery labs in 11/2020:
  - Total testosterone – 20 ng/dL (7 – 40 ng/dL)
  - Free testosterone – 10 ng/dL (1.1 -14.3 ng/dL)

Left adrenalectomy

- 12/2020 – Patient underwent laparoscopic left adrenalectomy
- Pathology:
  - Left adrenal mass; Benign adrenocortical nodules (X2, 3.8 cm and 2.3 cm), compatible with adrenocortical hyperplastic nodules.
- Discharged on morning dose of hydrocortisone 15 mg and 5 mg in evening.
- Cortisol level after holding hydrocortisone for 24 hours - 11.9 ug/dL
  - Hydrocortisone was discontinued

Post surgery follow up

- Patient was feeling better
  - Denied any fatigue, lightheadedness or dizziness
  - 16 pounds weight loss since surgery
  - Planned to go back to work in few weeks

- Right adrenal adenoma
  - Plan is to repeat dex suppression test in 6 months since it is possible that the second mass is also functional

References

- Agarwal et al. Combined Adrenal and Ovarian Venous Sampling to Localize an Androgen Producing Tumor. Cardiovasc Intervent Radiol (2010) 33:1266–1269.
- Evaluation and management of postmenopausal hyperandrogenism. Uptodate.
- Martin et al. Guidelines on Hirsutism. J Clin Endocrinol Metab, April 2018, 103(4):1233–1257.
- Markopoulos et al. Hyperandrogenism after menopause. European Journal of Endocrinology (2015) 172, R79–R91.
- Mattsson et al. Image in endocrinology: Testosterone-Secreting Ovarian Tumor Localized with (Fluorine-18)-2-Deoxyglucose Positron Emission Tomography. JCEM 91(3):738–739
- Peterson et al. The utility of adrenal and ovarian venous sampling in the investigation of androgen-secreting tumours. Internal Medicine Journal. 2011 Royal Australasian College of Physicians
- Pugeat et al. Recommendations for investigation of hyperandrogenism. Annales d'Endocrinologie 71 (2010) 2–7.
- Rothman et al. How should postmenopausal androgen excess be evaluated? Clinical Endocrinology (2011) 75, 160–164.
- Wang et al. Diagnosis and Localization of Testosterone-Producing Ovarian Tumors: Imaging or Biochemical Evaluation. Gynecologic Oncology 83, 596–598 (2001).
- Zeiger et al. American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons Medical Guidelines for the Management of Adrenal Incidentalomas. Endocr Pract. 2009;15(Suppl 1).