THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

AT THE FOREFRONT OF MEDICINE®

66 years old female with right adnexal mass

Endorama

Thaer Idrees M.D.

Second year adult endocrine fellow

February 2020

THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

AT THE FOREFRONT OF MEDICINE®

OBJECTIVES

- Review differential diagnosis of sex cord-stromal tumors
- Review the evaluation of such masses
- Pre - surgical management of pelvic masses
- Review the presentation, laboratory evaluation and the management of steroid cell tumor

HPI

- The patient is a 66 y/o female with PMH of DM2, HLD, HTN, and depression

  Chief complain: elective pelvic mass resection surgery

  Consult for: high cortisol
- *At the end of 2018, the patient noticed growing facial, chest, and leg hair*
- *She also noticed new adult-onset acne on her chin and neck*
- *PCP sent testosterone ➡ elevated*
- *Underwent transvaginal ultrasound, which showed a 14 cm pelvic mass*

PRE-OP AREA

	6 2/3/2020 0621
BASIC & COMPREHENSIVE	
Glucose, Ser/Plasma	*172 **
Sodium	*140*
Potassium, Ser/Plasma	*4.3 **
Chloride	*104*
Carbon Dioxide	*23*
Anion Gap	*13*
BUN	*12*
Creatinine	*1.2*
eGFR, Non-African ...	*49 **
eGFR, African Amer...	*57 **
Calcium	*9.2*
Inorganic Phosphate	*3.6*
Magnesium	*1.6*
Cortisol	*79.0 **

	1 1/14/2020 0854	2 4/13/2018 1209
DIABETIC SCREENING...		
Hb A1C	*12.4*	*6.0 **

High cortisol

Anesthesia called wondering about recs?

PMH:

- Bowel obstruction 1993
- Depression
- T2DM
- HLD
- HTN
- UTI

PSH:

- *Bowel obstruction secondary to a colonic mass requiring emergent partial colon resection in 1993 (benign).*
- *Hysterectomy*, total for uterus fibroids

PFH:

- Heart Disease: father
- No family history of DM

REVIEW OF SYSTEMS

- **Constitutional:** No fevers, no chills, no night sweats, no significant weight change
- **Eyes/Vision:** No visual changes, no eye discharge, no yellowing of eyes
- **ENT:** No coryza, no ear fullness or drainage, no throat pain or dysphagia
- **Cardiac:** No chest pain, no orthopnea, no PND, no peripheral swelling
- **Pulm:** No cough, no shortness of breath, no wheezing
- **GI:** No abdominal pain, no nausea, no vomiting, + loose stool , no melena or hematochezia
- **GU:** No dysuria, no hematuria, no change in urine output, no change in urine color
- **MSK:** +lower back pain
- **Skin:** No rash
- **Neuro:** No focal weakness, no difficulty with speech, no paresthesias

MORE HISTORY

- Was diagnosed with T2DM at the end of 2018 as well (when her symptoms started)
- Started on metformin 500 mg BID before lantus 20 U was added
- She noted some muscle weakness, easy bruising and worsening hypertension
- Noted decreased in her breasts size
- Increase in the size of her clitoris as well
- She was diagnosed with male pattern baldness and is using a wig

PHYSICAL EXAM

VS: weight: 185 lbs, BP: 124/68, HR: 74, RR: 13, temp: 97.2

- **General:** Not in distress, appears comfortable, cooperative, central obesity, no moon face
- **Eyes:** No conjunctival pallor or injection, no icterus
- **ENT:** membranes moist
- **Cardiac:** Regular rhythm, no murmurs, no rubs,
- **Pulm:** Clear bilaterally with adequate effort. No wheezes or crackles.
- **GI/Abd:** Not visibly distended, +TTP at midline incision; no rebound, no hepatosplenomegaly, no violaceous **striae**
- **GU:** No CVA tenderness or suprapubic tenderness
- **MSK:** Normal bulk and tone, no joint effusions or major deformities, no muscle weakness
- **Skin:** +midline abdominal incision, face and lower extimities with shaved hair, no
- **Neuro:** AAO x 3, PERRL, EOM normal, no facial asymmetry; no focal strength deficits; sensation grossly normal
- **Psych:** Normal insight, normal memory
- **Lymphatic:** No significant LAD
- **Extremities:** Warm, not diaphoretic

SH:

- Smoking status: former smoker

Meds:

- atorvastatin 10 mg
- cyanocobalamin (vitamin B-12)
- diclofenac 50 mg Oral
- ergocalciferol (50,000 unit) Oral capsule weekly
- HCTZ 25 mg daily
- insulin glargine (LANTUS) 20 units injection nightly
- metFORMIN ER 500 mg BID
- nystatin 100,000 unit/gram ointment
- traMADol (ULTRAM) 50 mg Oral tablet PRN

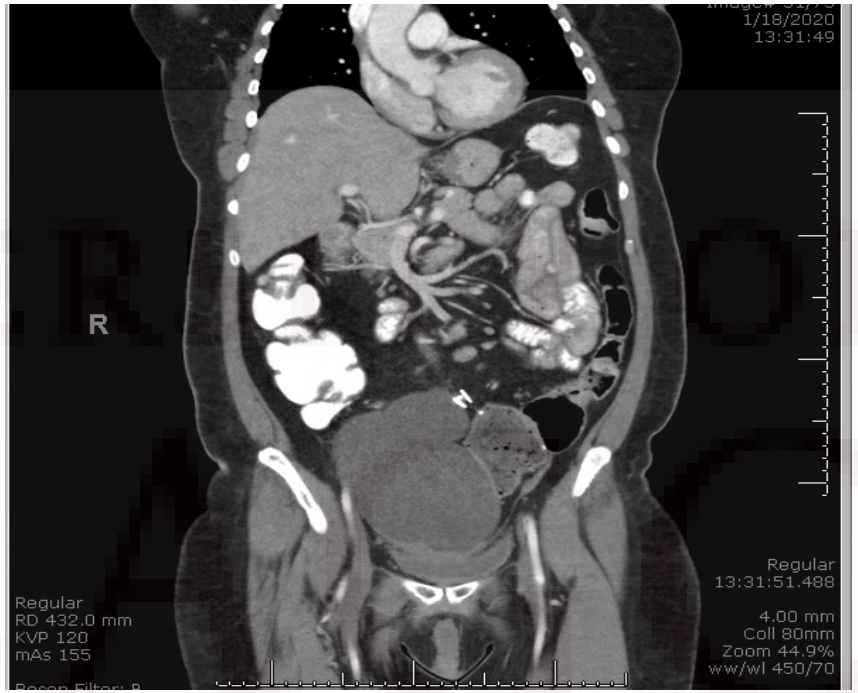
MRI 12/12/2020

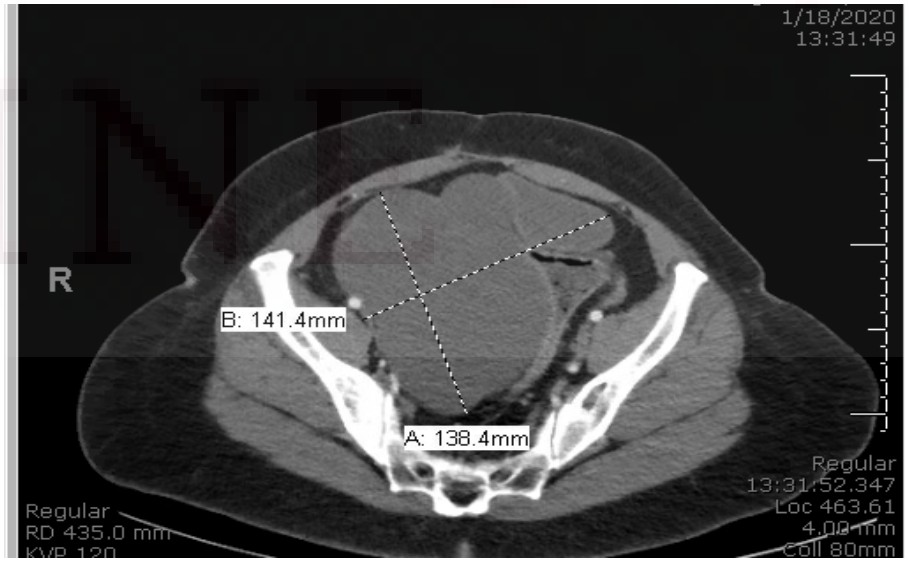
- Very large, multi lobulated right-sided pelvic/adnexal predominantly cystic pelvic mass, with contiguous involvement of the inferior aspect of the terminal ileum, and posterior urinary bladder
- There is secondary bilateral hydronephrosis and hydroureter due to mass effect
- The left ovary cannot be separately identified
- Surgical consultation recommended for a lesion this size, at risk for torsion

CT 1/19/2020

- UTERUS, ADNEXA: Uterus not visualized.
- BLADDER: Compressed by the large pelvic mass.
- LYMPH NODES: No significant abnormality noted.
- BOWEL, MESENTERY: **Large septated fluid density mass in the pelvis measured on series 201 image 113, 13.8 x 14.1 cm, unchanged from MRI of 12/12/2019. This exerts mass effect on the rectosigmoid and adjacent structures.**
- **ADRENAL GLANDS: No significant abnormality noted.**
- Sigmoid anastomosis. No free or loculated intraperitoneal fluid. No bowel wall thickening or dilatation

IMPRESSION: Large septated fluid density mass in the pelvis.





LABS

	6 2/3/2020 0621
BASIC & COMPREHENSIVE	
Glucose, Ser/Plasma	*172 **
Sodium	*140*
Potassium, Ser/Plasma	*4.3 **
Chloride	*104*
Carbon Dioxide	*23*
Anion Gap	*13*
BUN	*12*
Creatinine	*1.2*
eGFR, Non-African ...	*49 **
eGFR, African Amer...	*57 **
Calcium	*9.2*
Inorganic Phosphate	*3.6*
Magnesium	*1.6*
Cortisol	*79.0 **

	1 1/14/2020 0854	2 4/13/2018 1209
DIABETIC SCREENING...		
Hb A1C	*12.4*	*6.0 **

What other labs to send?

LABS

Te Binding Globulin	11 *
Calculated Free Te...	24 *
Total Testosterone	44
Test Information	The Total Test... *
DHEA-S	46.6 *

	July 2019	February 2020 (post op) 22:00
Free testosterone	68	24
Total testosterone	---	44
DHEA-S (9.40 - 246)	48	46.6 (9AM)
TSH	1.74	2.80
FT4	1.0	---

Component	Value	Ref Range & Units	Status
Total Testosterone	44	5 - 70 ng/dL	Final
Te Binding Globulin	11	nmol/L	Final
Comment:			
This test may be affected by biotin interference. Patients on high dose biotin (5mg/day or more) should not have samples drawn until at least 24 hours after the last biotin administration.			
Albumin	3.4 ↓	3.5 - 5.0 g/dL	Final
Calculated Free Testosterone	24	pg/mL	Final
Comment:			
Free testosterone reference ranges for children and women were derived from normative data established in carefully screened children (6-11 yrs old) and young women (11-40 yrs old, eumenorrheic, nonhirsute, with ultrasonographically normal ovaries). The normal upper limit (95th percentile) of free testosterone is expected to be <3.0 pg/mL in prepubertal children and up to 9.0 pg/mL in women. For pubertal children, free testosterone values are intermediate and fall between prepubertal and adults values and overlap with both.. For aging men and post-menopausal women, values fall proportionally as much as or more than total testosterone.			
Test Information			Final
The Total Testosterone test was developed and its performance characteristics determined by the UCH Section of Clinical Chemistry. It has not been approved by the FDA.			
Comment:			
The UCH Section of Clinical Chemistry is regulated under CLIA and is qualified to perform high complexity testing. This test should only be used for clinical purposes and should not be regarded as investigational or for research.			

HIRSUTISM

- The majority of hirsutism is due to androgen excess ($80%)
- (70% to 80%) have PCOS (Gonadotropin-dependent functional ovarian hyperandrogenism)
- Idiopathic hirsutism constitutes 5% to 20% of hirsute women
- NCCAH: 4.2% of hyperandrogenic women
- Androgen-secreting tumors: 0.2% of hyperandrogenic women
- Clinicians must consider Cushing syndrome, acromegaly, hypothyroidism, and (rarely) hyperprolactinemia
- Consider topical androgen use by a partner, exogenous androgens or anabolic steroids, or valproic acid

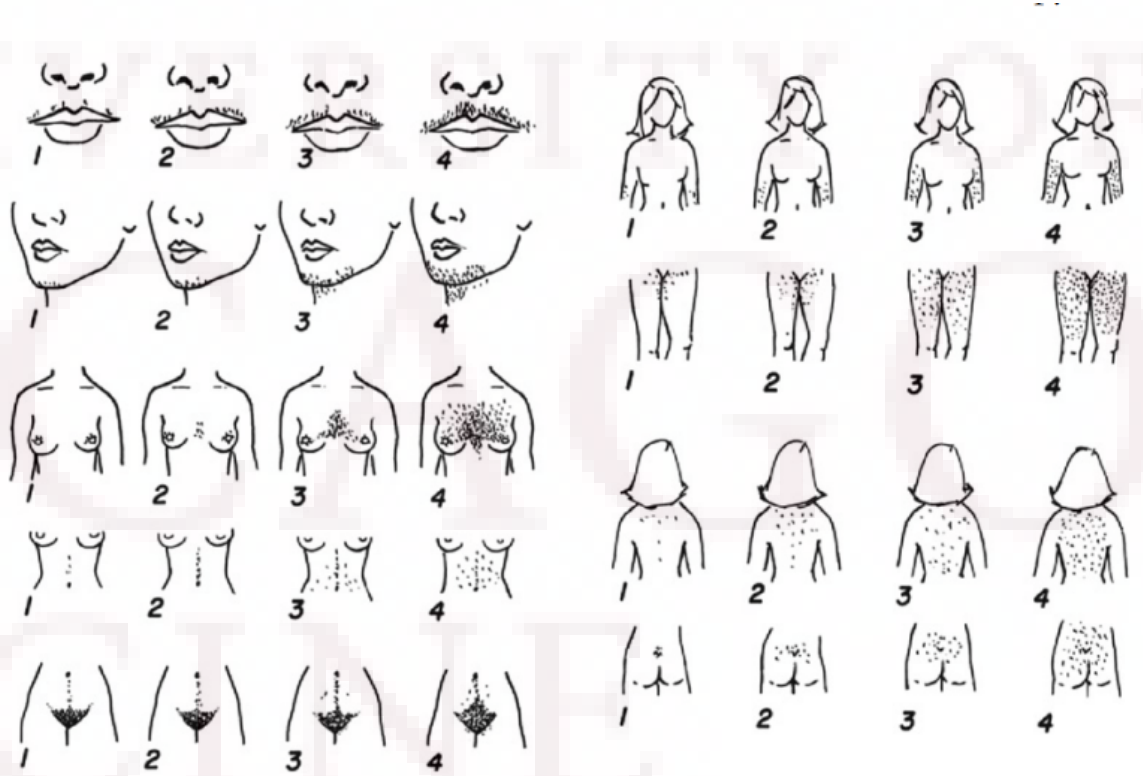


Figure 1. Ferriman–Gallwey hirsutism scoring system (4). Each of the nine body areas most sensitive to androgen is assigned a score from 0 (no hair) to 4 (frankly virile). These separate scores are summed to provide a total hormonal hirsutism score. Generalized hirsutism (score ≥8) is abnormal in the general US population, whereas locally excessive hair growth (score <8) is a common normal variant. The normal score is lower in some Asian populations and higher in Mediterranean populations (see text). Reproduced from Hatch *et al.* (5).

Martin KA et al.,. J Clin Endocrinol Metab. 2018

BACK TO THE PATIENT

FINAL PATHOLOGIC DIAGNOSIS

B. Right fallopian tube and ovary; salpingo-oophorectomy:
- Ovary with steroid cell tumor, not otherwise specified (1.0 cm) and rete cystadenoma (7.5 cm)
- Fallopian tube without diagnostic abnormality

B. Right ovary and Overall size: 9 x 6 x 0.8 cm
Smooth, glistening- Solid Lesion: 1 x 0.9 x 0.5 cm yellow, firm, well-circumscribed mass immediately adjacent to atrophic appearing ovary-Cystic component: Unilocular, smooth walled, deflated cyst measuring 7.5 x 6 cm

- Sertoli-Leydig cell tumors group (androblastoma)
  - Well-differentiated
  - Of intermediate differentiation
    - variant with heterologous elements
  - Poorly differentiated (sarcomatoid)
    - variant with heterologous elements
  - Retiform
    - variant with heterologous elements
- Sertoli cell tumor
- Stromal-Leydig cell tumor

Sex cord-stromal tumors of mixed or unclassified cell types

- Sex cord tumor with annular tubules
- Gynandroblastoma
- Sex cord-stromal tumor, unclassified

Steroid cell tumors

- Stromal luteoma
- Leydig cell tumor group
  - Hilus cell tumor
  - Leydig cell tumor, non-hilar type
  - Leydig cell tumor, NOS
- Steroid cell tumor, NOS
  - Well-differentiated
  - Malignant

WHO, World Health Organization; NOS, not otherwise specified.

SEX CORD TUMORS

- Originate from the dividing cells support and surround the oocytes, including the cells that produce ovarian hormones (granulosa cells, theca cells, Sertoli cells, Leydig cells, and fibroblasts)

- Ovarian steroid cell tumors comprise < 0.1% of all ovarian tumors

<u>three subtypes:</u>

- stromal luteoma
- Leydig cell tumor
- steroid cell tumor not otherwise specified (NOS)

Horta M et al., Diagn Interv Radiol. 2015

Young RH et al.,. Mod Pathol. 2005

PRESENTATIONS

CASE SERIES

Ovarian Steroid Cell Tumors (Not Otherwise Specified)

A Clinicopathological Analysis of 63 Cases

Mary C. Hayes, M.D., and Robert E. Scully, M.D.

- 63 steroid cell tumors, not otherwise specified
- Age: 2 to 80 years
- most common initial manifestation was virilization (41%)
- four patients had estrogenic manifestations
- four patients had Cushing's syndrome
- Tumors: 6% bilateral, 1.2 to 45 cm in greatest dimension
- Follow-up data ranging from 1 to 19 years (average 5.2 years) in duration were available for 50 patients:
- In 24 cases, the tumor was designated probably benign (no evidence of spread beyond the ovary within 3 or more years postoperatively)
- In 18 patients, the tumor was clinically malignant. The best pathological correlates of malignant behavior were: the presence of two or more mitotic figures per 10 high power fields (92% malignant); necrosis (86% malignant); a diameter of 7 cm or greater (78% malignant); hemorrhage (77% malignant); and grade 2 or 3 nuclear atypia (64% malignant)

Hayes MC et. el.,Am J Surg Pathol. 1987.

CASE REPORT 1

- Young woman was found to have a lesion during the study of infertility
- It was submitted to laparoscopic cystectomy: ovarian steroid cell tumor as histological finding
- Analytically she had **normal** blood count and hormonal assay [FSH, LH, TSH, free T4, testosterone, and dehydroepiandrosterone (DHEA)
- A transvaginal ultrasonography was performed revealing a normed uterus and ovaries slightly enlarged and polycystic with a small echogenic mass in the right ovary of **15 millimeters**
- Pathological: ovarian steroid cell tumor NOS, no features predictive of malignancy
- At 24 months, she had no evidence of recurrence

Alves P et al., Case Rep Obstet Gynecol. 2019

CASE REPORT 2

- 17 y.o girl with the complaint of amenorrhea
- DHEA-S= 5.9 µmol/L (0.49-8.71 µmol/L).
- CT pelvic scan: a solid, right ovarian tumor and detected no adrenal gland enlargement or additiona tumors
- Pathology: benign ovarian steroid cell tumor, NOS

Laboratory analysis before and after surgery

	Before surgery	4 days after surgery	1 month after surgery	Normal values
Hemoglobin	157	132	125	115-150 g/L
Testosterone	14.28	0.97	2.37	0.35-2.6 nmol/L
CA125	16.5	-	19	< 35 U/ml
CA199	17.37	-	15.19	< 39 U/ml
HE-4	46.06	-	39.76	< 140 pmol/L
CEA	0.68	-	0.50	< 4.7 ng/ml
AFP	1.24	-	1.25	< 20 ng/ml
CA724	1.51	-	1.32	< 6.90 U/ml
Premenopausal ROMA	6.24	-	4.52	< 11.4%

Yuan X et al., *Int J Clin Exp Pathol*. 2019

CASE REPORT 3

- 55-year-old, postmenopausal patient who presented with complaints of vaginal bleeding and abdominal pain
- History of excessive hair growth since 3-4 years
- Ultrasonography revealed a solid right ovarian mass 9x6x3.5cm with a possibility of ovarian sex cord tumor
- Histopathology: steroid cell tumor, NOS type
- No labs provided

Bhagat R et al. *J Clin Diagn Res*. 2016;

CASE REPORTS

Case 1:

- 23-year-old female presented with increasing facial and truncal hair, acne, amenorrheic, virilizing symptoms, atrophy of the breasts
- Normal values of FSH, LH, prolactin and cortisol
- Total serum testosterone was 3.68 ng/ml (0.15-0.51 ng/ml),
- DHEA-S = 403.1 μg/dl (19-391 μg/dl)
- Total testosterone normalized within normal limits 7 days after surgery

Case 2:

- 21-year-old unmarried woman because of a 7-year secondary amenorrhea history, bilateral pelvic mass (20 cm, 15 cm), increasing hirsutism, acne, deepening voice, and acanthosis nigricans-like change of skin
- High testosterone 5.38 ➔ 13.2 (0.15-0.51 ng/ml)
- Tumor cells with irregular nuclei or atypia were identified, 4 cycles of standard PVB (cisplatin, vincristine and bleomycin, every three weeks) chemotherapy
- Deceased of tumor recurrence in pelvic and abdominal cavity 10 months after operation

Jiang W. et al., *J Ovarian Res*. 2013

CASE REPORT 6

- 46 y.o woman presented with secondary amenorrhea and virilization symptoms for 1 year + Cushingoid symptoms
- Physical examination revealed hirsutism of the chin, excess hair growth on abdomen and clitoral hypertrophy
- Pathology: ovarian steroid cell tumor (NOS) without malignant behavior
- Cushing syndrome regressed and hirsutism disappeared completely 4 months Post-op
- 1-year testosterone normalized

	Before surgery				
Hormone	Baseline	After 4 mg Dex	After 16 mg Dex	After surgery	Normal values
Serum cortisol					
8 AM	555.46	544.55	556.31	<25.7	198.7–797.5 nmol/L
4 PM	577.23			<25.7	85.3–459.6 nmol/L
0 AM	576.38			<25.7	0–165.7 nmol/L
Plasma ACTH					
8 AM	<1.1	1.36	2.73	3.49	<10.12 pmol/L
4 PM	1.42			3.6	
0 AM	<1.1			1.89	
Urinary-free cortisol	1742.2	964.5	1670.9	102	98.0–500.1 nmol/24 h
Serum testosterone	36.83	33.69	34.86	<0.35	0.5–2.6 nmol/L
Serum 17-OHP	2.347	3.234	2.842	0.057	0.1–0.8 ng/dL
Serum DHEA	491	447	606	<15	35–430 μg/dL

17-OHP = 17-hydroxyprogesterone, ACTH = adrenocorticotropic hormone, DHEA = dehydroepiandrosterone.

Zang L et al., *Medicine (Baltimore)*. 2017

Another case report measured: Androstendion **24.90** (0.40–3.40 ng/ml)

Szeliga, A et al., 2019

Another case report measured: hypercortisolismn and hyperprolactinemia and hyperestrogenemnia. All hormone abnormalities were resolved after Salpingo-Oopherectomy

Abebe S et al., 2010

CASE REPORT

- ACTH-producing ovarian steroid cell tumor, NOS, causing ectopic ACTH syndrome in a prepubertal girl
- 6 -year-old girl presented with a 5-month history of rapid weight gain of 7 kg
- Two months prior, she developed facial acne, round facie, and hirsutism
- Weight was 27.2 kg (97th percentile)
- Serum testosterone 56 ng/dl (3–10 ng/dl)
- DHEA-S 156 lg/dl, 4.2 lmol/l (19–144 lg/dl)

High dose dexamethasone suppression test

Day	24 h urine free cortisol (normal range 3–9 µg/24 h, 8.3–24.8 nmol/day)	Serum cortisol (normal range 3–21 µg/dl, 83–579 nmol/l)	Serum ACTH (normal range 10–60 pg/ml, 2.2–13.3 pmol/l)
0	657.45 µg/24 h (1,814 nmol/day)	38.93 µg/dl (1,073 nmol/l)	402.40 pg/ml (89.4 pmol/l)
1	1036.07 µg/24 h (2,858 nmol/day)	44.8 µg/dL (1,234 nmol/l)	N/A
2	Missing specimen	50.42 µg/dl (1,389 nmol/l)	278.40 pg/ml (61.9 pmol/l)

HOW TO TREAT THESE TUMOR IN CASE RECURRENCE WAS DETECTED

TREATMENT WITH GNRH

- 50 y.o female presented with hirsutism and was found to have SCT- NOS
- Testosterone level was 882 ng/dl (HH)
- Underwent surgical resection, but CT detected liver mets 5 years after the initial surgery
- Started on chemotherapy: bleomycin, etoposide, and cisplatin (D/c due to prolonged neutropenia and peripheral neuropathy)
- Testosterone elevated to 448 ng/ml 1 month after the D/c
- Immunohistochemical analysis of her primary tumor showed positive staining for GnRH receptor in the cytoplasm, a GnRH was attempted (leuprorelin 1.88 mg IM intramuscularly every month)
- Testosterone immediately normalized after three cycles of GnRHa
- CT scan confirmed a 28.6% reduction of the tumor size
- Adverse events were not observed and her hirsutism and virilization were improved
- Tumor sizes further decreased, and GnRH continued

Nakasone T et al., *Gynecol Oncol Rep*. 2019

BACK TO THE PATIENT

BACK TO PT

- Cortisol after holding hydrocortisone for 24 hrs, was 14 (8 am) (Vs. 77)
- VS maintained stable and she felt great off hydrocortisone for more than 3 days
- She was discharged on no hydrocortisone
- Was sent home on metformin 500 mg BID and lantus 10 U
- Scheduled to see us in few weeks
- Will schedule BMD
- Re-measure testosterone, cortisol, and A1c

KEY POINTS

- Steroid cell tumors, NOS, are rare ovarian tumors which can be difficult to diagnose
- Surgical intervention is the most effective treatment for steroid cell tumors (NOS)
- The co-secretion of cortisol and androgen are extremely rare and represent a real diagnostic challenge for both clinicians and pathologists
- Labs to send: total/free testosterone, DHEA, 17-OHP , cortisol, 24 hrs cortisol, progesterone, aldosterone, and androstendion
- CA19-9, CA125 were found to be normal
- About 25% without no increase in the level of hormones
- Malignant behavior in 1/3 of cases (Kurman et al., 2014)
- Hayes et al. reported malignant behaviors 18 out of 63 cases
- GnRH-agonist may be required when persistent abnormal serum hormone levels, the doubt of residual tumor, recurrences or metastases are noted

REFERENCES

- Martin KA, Anderson RR, Chang RJ, Ehrmann DA, Lobo RA, Murad MH, Pugeat MM, Rosenfield RL. Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018 Apr 1;103(4):1233-1257. doi: 10.1210/jc.2018-00241. PubMed PMID: 29522147.
- Young RH. Sex cord-stromal tumors of the ovary and testis: their similarities and differences with consideration of selected problems. Mod Pathol. 2005 Feb;18 Suppl 2:S81-98. Review. PubMed PMID: 15502809.
- Szeliga, A., Zysnarska, A., Podfigurna, A., Maciejewska-Jeske, M., Moszyński, R., Sajdak, S., ... Męczekalski, B. (2019). *Ovarian steroid cell tumor as an example of severe hyperandrogenism in 45-year-old woman. Gynecological Endocrinology, 1–5.* doi:10.1080/09513590.2019.1689551
- Abebe S, Erkie M, Feleke Y. A case report of steroid cell tumour of the ovary--not otherwise specified variant with hyperandrogenism, hypercortisolism, hyperprolactinemia and hyperestrogenemia. Ethiop Med J. 2010 Jan;48(1):67-72. PubMed PMID: 20608001.
- Bhagat R, Bodal VK, Gupta N, Garg P. Steroid Cell Tumor of Ovary - A Rare Case Report. J Clin Diagn Res. 2016;10(9):ED06–ED07. doi:10.7860/JCDR/2016/15767.8556 Alves P, Sá I, Brito M, Carnide C, Moutinho O. An Early Diagnosis of an Ovarian Steroid Cell Tumor Not Otherwise Specified in a Woman. Case Rep Obstet Gynecol. 2019 Jan 16;2019:2537480. doi: 10.1155/2019/2537480. eCollection 2019. PubMed PMID: 30792930; PubMed Central PMCID: PMC6354154.
- Zang L, Ye M, Yang G, et al. Accessory ovarian steroid cell tumor producing testosterone and cortisol: A case report. Medicine (Baltimore). 2017;96(37):e7998. doi:10.1097/MD.0000000000007998
- Jiang W, Tao X, Fang F, Zhang S, Xu C. Benign and malignant ovarian steroid cell tumors, not otherwise specified: case studies, comparison, and review of the literature. *J Ovarian Res*. 2013;6:53. Published 2013 Jul 22. doi:10.1186/1757-2215-6-53
- Yuan X, Sun Y, Jin Y, et al. Ovarian steroid cell tumor, not otherwise specified, treated with surgery: a case report and review of literature. *Int J Clin Exp Pathol.* 2019;12(4):1434–1438. Published 2019 Apr 1.
- Hayes MC, Scully RE. Ovarian steroid cell tumors (not otherwise specified). A clinicopathological analysis of 63 cases. Am J Surg Pathol. 1987Nov;11(11):835-45. PubMed PMID: 2823622.
- Nakasone T, Nakamoto T, Matsuzaki A, Nakagami H, Aoki Y. Direct evidence on the efficacy of GnRH agonist in recurrent steroid cell tumor-not otherwise specified. Gynecol Oncol Rep. 2019;29:73–75. Published 2019 Jul 16. doi:10.1016/j.gore.2019.07.006

THANK YOU

Questions/comments?