

THE UNIVERSITY OF  
MEDICINE

# A 36 YEAR-OLD FEMALE WITH HIRSUTISM

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# HISTORY OF THE PRESENT ILLNESS

- 36 year-old African-American female presents to her OB-GYN with:
  - **Oligomenorrhea**
    - Menarche at age 14
    - Cycles were always irregular; last 2-3 days with no interval bleeding
    - LMP was ~2 weeks before this visit, however, had not had a period for the last year prior to this one
    - Oral contraceptive use since teen years – admits to recent non-compliance
    - Pregnancy history: Spontaneous pregnancy 12 years ago → abortion, no sexual activity since that time
  - **Male pattern boldness** for the last 12 years
  - **Facial hair** for the last 12 years – shaves once per month

# PERTINENT HISTORY

## Family History

- Type 2 DM
  - Mother
- Hypertension
  - Two brothers
- Sarcoidosis
  - Maternal aunt
  - Maternal grandmother
- Negative for hirsutism, infertility, menstrual irregularities

## Social History

- Never married
- Lives with mother
- Not sexually active
- Denies alcohol, drug, or tobacco use

# PAST MEDICAL HISTORY

- **Morbid Obesity**
  - Gradual weight gain – morbidly obese over the last 10 years
- **Polycystic Ovarian Syndrome**
  - Previously on Metformin 500 mg daily and oral contraception (non-adherent)
- **Hypertension**
  - Hydrochlorothiazide 50 mg daily
  - Metoprolol-XL 25 mg daily
  - Enalapril 20 mg daily
- **Obstructive sleep apnea**
  - Non-adherent to CPAP therapy
- **Schizophrenia/Depression**
  - Aripiprazole 15 mg daily
  - Aspirin 81 mg daily

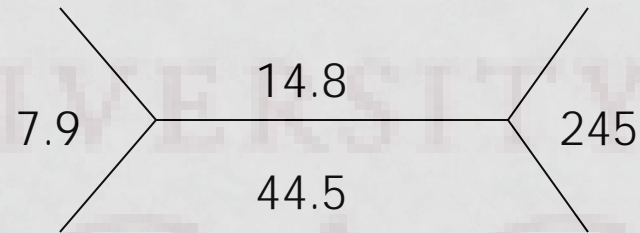
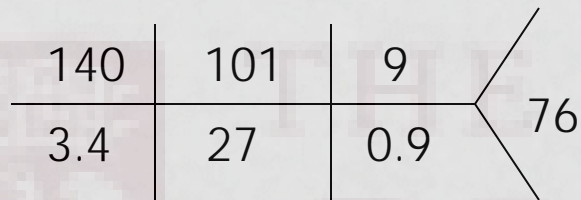
# REVIEW OF SYSTEMS:

- **Constitutional:** Denies weight change, fevers, chills, weakness. +**fatigue and obesity.**
- **Eyes:** Denies blurry vision, diplopia. No visual field deficit.
- **ENT:** Denies rhinorrhea, tinnitus, difficulty swallowing. Denies change in voice.
- **Respiratory:** Denies shortness of breath, cough.
- **Cardiovascular:** Denies chest pain, palpitations, lower extremity edema.
- **Gastrointestinal:** Denies nausea, vomiting, abdominal pain, diarrhea, abdominal striae.
- **Genitourinary:** Denies urinary changes. + **Oligomenorrhea.**
- **Musculoskeletal:** Denies arthralgias or myalgias.
- **Skin:** Denies rash, acne. + **Facial hair. + Male pattern baldness.**
- **Neurological:** No headaches, tremors, or weakness.

# PHYSICAL EXAMINATION

- **Vitals:** BP 135/87, Pulse 115, Ht 170.2 cm (5' 7"), Wt 156.219 kg (344 lb 6.4 oz), BMI 53.94.
- **General:** Well-appearing female in no apparent distress.
- **Eyes:** Non-injected sclera. Pupils equal, round, and reactive.
- **Neck:** There is thyromegaly and thyroid nodules are not appreciated. Skin tags are absent. **Acanthosis nigricans is noted.**
- **Respiratory:** Clear to auscultation bilaterally.
- **Cardiovascular:** Tachycardic. Regular rhythm. No lower extremity edema.
- **Abdomen:** Normoactive bowel sounds. Soft, non-tender. **Obese abdomen with no violaceous striae.**
- **Genitourinary:** **Noted to have clitoral enlargement by Gyn service exam.**
- **Skin:** No rash. No acne is present. **Male pattern balding. Hair on chin, side of face, shaved.**
- **Musculoskeletal:** Normal gait and station.
- **Psychiatric:** Alert and oriented x3. Appropriate mood/affect.

# DIAGNOSTIC EVALUATION



Calcium 9.3 (8.4-10.2 mg/dL)

10/23/2013	
Prolactin	8.69 (4.8 - 23.3 ng/mL)
Total testosterone	174 (20 - 60 ng/dL)
Free testosterone	55 (3 - 9 pg/mL)
Te binding globulin	30 (20 - 100 nmol/L)
DHEA-SO4	117 (45 - 270 ug/dL)

**TABLE 1.** Prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism

	No. of patients	% of total no. of patients
Classic PCOS	538	56.6
Ovulatory PCOS	147	15.5
Idiopathic hyperandrogenism	150	15.8
Idiopathic hirsutism	72	7.6
NCAH	41	4.3
Androgen-secreting tumors	2	0.2

Carmina E, Rosato F, Janni A, Rizzo M, Longo RA. Relative prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism. *J Clin Endocrinol Metab.* 2006;91(1):2-6.

**Table 1** Differential diagnosis of clinical hyperandrogenism.

Diagnosis	Frequency (%)	Age of onset years	Time of onset to presentation	Menstrual disturbance	Virilization
PCOS and related disorders	>95	15–25	Years	+/-	Rare
CAH	1–2	Congenital	Birth/adolescence/adulthood	+	+/-
Adrenal tumour	<1	Any time	Weeks–months	+	+
Ovarian tumour	<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.

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.



# PERTINENT PRIOR LABS (2008)

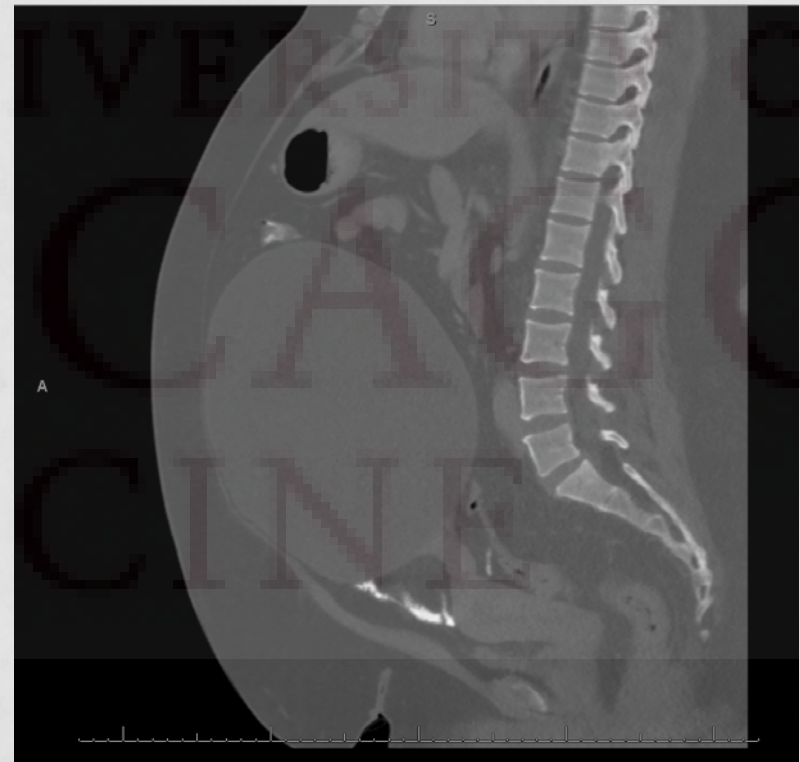
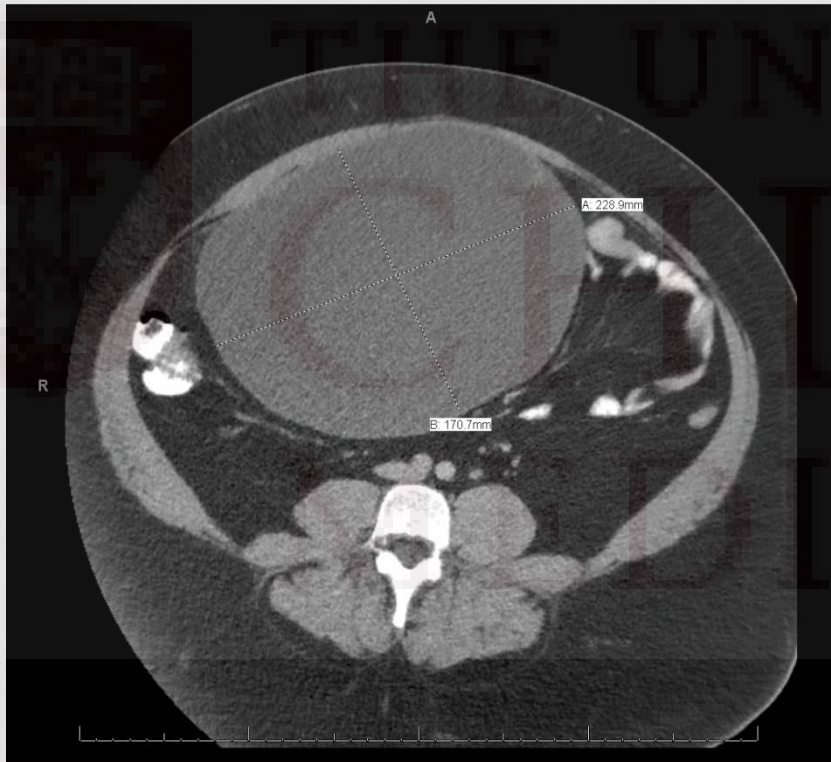
Total testosterone	179 (19 - 70 ng/dL)
Free testosterone	59 (3 - 10 pg/mL)
Te binding globulin	10 (12 - 63 nmol/L)
DHEA-SO4	73 (45 - 270 ug/dL)

Prolactin	7.0 (4.8 - 23.3 ng/mL)
LH	8 (Follicular: 2.4-12.6 mIU/mL Mid-Cycle: 14.0-95.6 mIU/mL Luteal: 1.0-11.4 mIU/mL)
FSH	6 (Follicular: 3.5-12.5 mIU/mL Mid-Cycle: 4.7-21.5 mIU/mL Luteal: 1.7-7.7 mIU/mL)
TSH	1.4 (0.30 - 4.00 mcU/mL)

# PELVIC ULTRASOUND

- Uterus is normal in size and contour
- Endometrial thickness - 5.7 mm
- Cervix is normal in appearance
- Left ovary was not visualized
- Right ovary appears normal
  - A large cystic mass is seen within the right adnexal area measuring 239 x 197 x 229 mm with septations

# CT ABDOMEN



# DIAGNOSTIC IMPRESSION

- Given adnexal mass with increased testosterone level, and findings of male-patterned baldness, facial hair, and clitoral enlargement – Sertoli-Leydig ovarian tumor is suspected
- Referred to Gyn-Onc for surgical management

# PATHOLOGY

- Left salpingo-oophorectomy
  - **Mature cystic teratoma**
    - Contains mature respiratory and intestinal epithelium with smooth muscle
    - Small component of squamous cystic structure (dermoid cyst)
    - Mature adipose tissue, cartilage, and glial tissue also present
  - **Hyperthecosis and edema**
    - Distinct from teratoma
    - Inhibin, calretinin, melan A all positive

# Coexistence of Mature Teratoma and Thecoma in an Ovary

## A Report of Two Cases

Yosuke Morimitsu<sup>1</sup>, Osamu Nakashima<sup>1</sup>, Masayoshi Kage<sup>1</sup>,  
Masamichi Kojiro<sup>1</sup>, Katsuichi Kawano<sup>2</sup>, and Toshihiko Koga<sup>3</sup>

Two cases of coexisting mature teratoma and thecoma are reported. In Case 1, a 36-year-old woman presented with severe genital bleeding and an ovarian tumor, 12×9 cm in size, was found. In Case 2, a 48-year-old postmenopausal woman presented with severe lower abdominal pain and an ovarian tumor, 15×11 cm in size, was detected. Macroscopically, the resected tumors of both cases showed a unilocular cystic tumor adjacent to a solid tumor. Microscopically, the cystic tumors were composed of cutaneous tissues and the solid tumors consisted of spindle cells with lipid-rich cytoplasm, arranged in interlacing bundles. The cystic tumor and the solid tumor were completely separate and no transitional features were recognized histologically. *Acta Pathol Jpn* 41 : 922-926, 1991.

**Key words :** Mature teratoma, Thecoma, Ovary

### CASE REPORTS

#### Case 1

A 36-year-old woman with a history of 4 pregnancies and 3 deliveries was admitted as an emergency case on March 1, 1988 because of severe genital bleeding. An abdominal mass had been pointed out one year previously. Her preceding menstrual period was about two weeks previously. Physical examination revealed an enlarged abdominal mass. There were no remarkable changes in the laboratory data except for slight anemia. Laparotomy was performed on March 17, 1988. At operation, a right ovarian tumor, 12×9 cm in size, was found in Douglas's cavity. The uterus was 9 cm in the greatest dimension with no remarkable change. The left

# POST-OPERATIVE EVALUATION

12/11/2013	
Total testosterone	51 (20 - 60 ng/dL)
Free testosterone	14 (3 - 9 pg/mL)
Te binding globulin	38 (20 - 100 nmol/L)

- Menstrual cycles returned in 01/2014.

# LABS 03/2014:

Total testosterone	30 (20 - 60 ng/dL)
Free testosterone	9 (3 - 9 pg/mL)
Te binding globulin	32 (20 - 100 nmol/L)
DHEA-SO4	112 (45 - 270 ug/dL)

Prolactin	7.0 (4.8 - 23.3 ng/mL)
LH	2.8 Follicular: 2.4-12.6 mIU/mL Mid-Cycle: 14.0-95.6 mIU/mL Luteal: 1.0-11.4 mIU/mL
FSH	1.2 Follicular: 3.5-12.5 mIU/mL Mid-Cycle: 4.7-21.5 mIU/mL Luteal: 1.7-7.7 mIU/mL
Estradiol	115 (30-400 pg/mL)
17-OH Progesterone	149 Follicular: < 80 ng/dL Luteal < 285 ng/dL
Cortisol	8.2 mcg/dL
ACTH	45 pg/mL

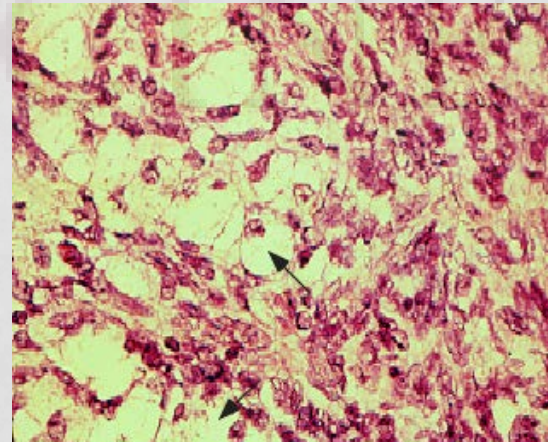
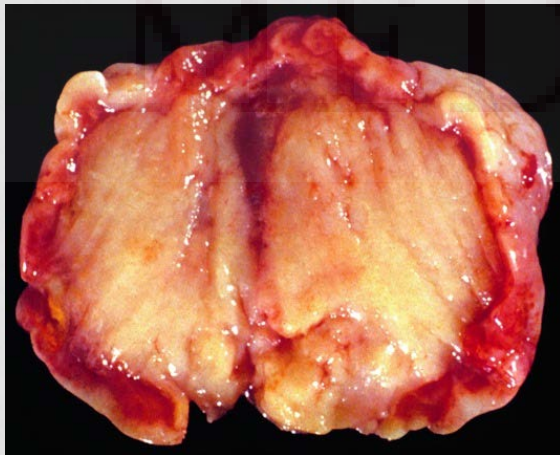


# CLINICAL REVIEW

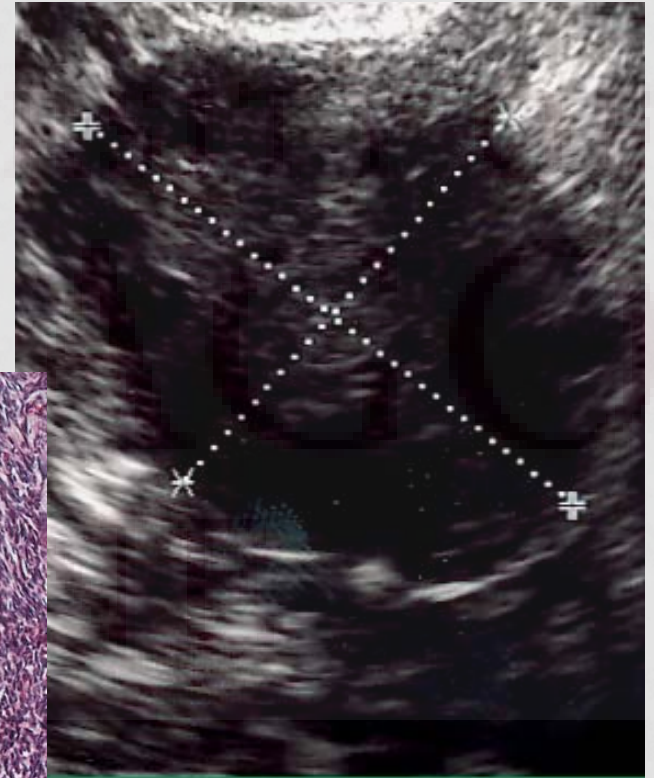
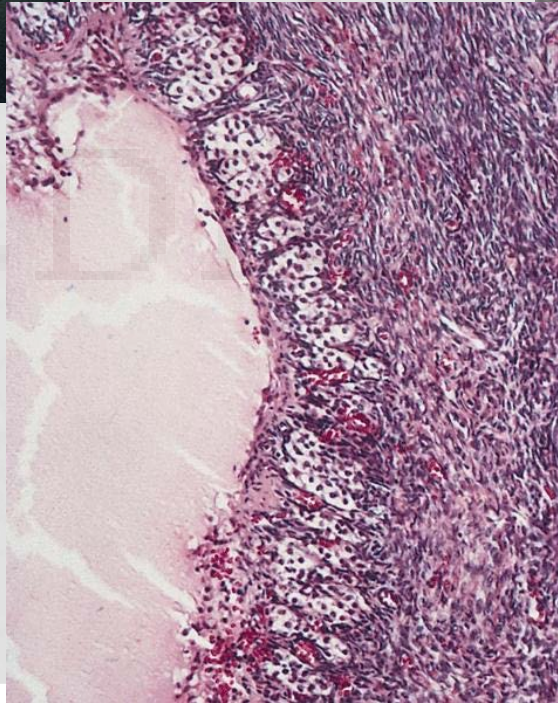
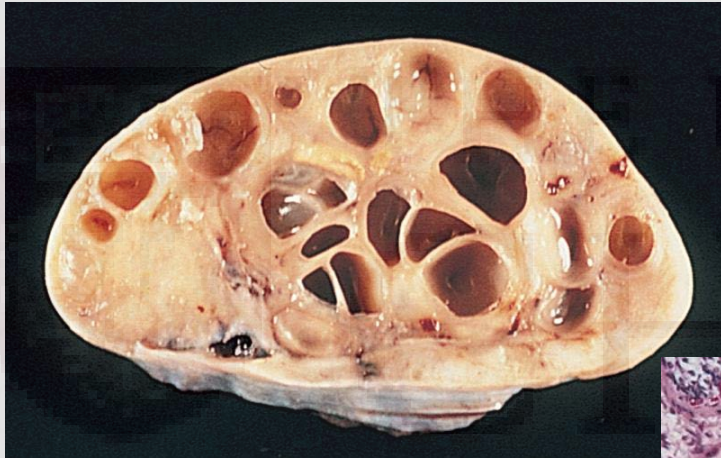
- Diagnosis and management of ovarian hyperthecosis
  - Disorder of severe hyperandrogenism and insulin resistance
  - Predominately occurs in postmenopausal women
  - Women often present with slowly progressive acne and hirsutism and likely to be virilized
- Treatment of infertility in ovarian hyperthecosis

# HYPERTHECOSIS

- Refers to presence of nests of luteinized theca cells in the ovarian stroma
- Occurs due to differentiation of the ovarian interstitial cells into steroidogenically active luteinized stromal cells



# POLYCYSTIC OVARY SYNDROME



# DIFFERENTIATION FROM PCOS

**Table 2** Features atypical of polycystic ovarian syndrome which should prompt comprehensive evaluation.

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Presentation outside the age of 15–25 years

Rapid progression

< 1 year between hirsutism being noticed and seeking medical advice

Presence of virilization

Testosterone levels

Total > twice upper limit of normal

Index of free testosterone > 4 times upper limit of normal

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# BIOCHEMICAL FINDINGS

- Serum total testosterone concentrations  $>150$  ng/dL ( $>5.2$  nmol/L)
  - Most important biochemical finding; should consider imaging of adrenals and ovaries to identify source of androgen production
- Insulin resistance and hyperinsulinemia → may be severe
- Normal levels of
  - LH/FSH (may also be suppressed)
  - DHEA or DHEA-S
  - Prolactin and IGF-1
  - Normal 17(OH) progesterone concentrations
    - Basal  $<6$  nmol/L (200 ng/dL)
    - 60 minutes post-ACTH (250 mcg)  $<30$  nmol/L (1000 ng/dL).

# IMAGING FINDINGS

- Bilateral increase in ovarian stroma or multifollicular appearance in PCOS
- Ovarian enlargement
  - Sometimes up to 3-4 times above the normal size

# MANAGEMENT

## In premenopausal women:

- ❖ Treatment of hirsutism predominately by local therapy, OCP, anti-androgens or GnRH-agonists in combination with estrogen-progestin replacement
- ❖ Weight reduction and management of insulin resistance
- ❖ No clinical trials on infertility management
  - ❖ Clomiphene and gonadotropins can be tried

## In postmenopausal women:

- ❖ Bilateral oophorectomy
- ❖ Long-term GnRH-agonist treatment, particularly in women who have are high risk surgical candidates due to comorbidities or who are unwilling to undergo bilateral oophorectomy

# GNRH-AGONIST TREATMENT:

	Patient no.	Baseline	8 weeks	16 weeks	24 weeks
Hair growth score (Ferriman and Gallwey scale)	2	22	22	15	10
	3	13	13	8	8
	4	30	28	24	19
Testosterone (nmol/l)	2	5.3	0.7	0.6	0.5
	3	6.0	1.3	1.5	1.7
	4	8.9	2.4	1.9	2.2
Cholesterol (mmol/l)	2	5.8	–	–	–
	3	7.3	7.1	7.2	7.0
	4	6.0	5.9	7.3	5.9
Triglycerides (mmol/l)	2	3.5	–	–	–
	3	3.0	4.5	5.4	4.0
	4	4.8	5.0	5.9	4.9



# RETURNING TO OUR PATIENT

- Patient was not interested in having children and wanted to consider options for permanent sterility
  - Potential Options
    - Tubal ligation?
    - Oophorectomy +/- tubal ligation?
    - Essure?
- Metabolic syndrome/insulin resistance?
  - Hgb A1c 5.9
  - LDL 128; HDL 43; TG 91

# CONCLUSIONS

- **Hyperthecosis** is the presence of nests of luteinized theca cells in the ovarian stroma resulting from differentiation of ovarian interstitial cells into steroidogenically active luteinized stromal cells
- It is a very rare condition

# REFERENCES:

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