Case # 1

50 year-old man

presents with gynaecomastia
Medical History

- asthma, nasal allergy
- viral hépatitis at the age of 25
- recent intercostal zona
- married
- 2 healthy children
- informatician

**Familial History:**

- thyroid disease in the father and grand mother
Current problems

slow-onset gynaecomastia since ± 2 years
bilateral, asymmetric  L > R
tender
+ loss of libido and erectile dysfunction

+ weight gain of 10 kg in 5 - 6 years
(84 kgs 2004,  94 kg 2010)
Clinical examination

92.6 kg   1.89 m   BMI 25.8 kg/m$^2$ waist 100 cm
BP 12/6   HR 80/min

general examination normal

bilateral gynaecomastia
normal sex characters
Other questions?

Other examination?
Treatment

- Atarax - Xyzall
- Symbicort when needed

- no medication known to induce gynaecomastia
Clinical examination

92.6 kg  1.89 m  BMI 25.8 kg/m²  waist 100 cm
BP 12/6  HR 80/min

general examination normal

bilateral gynaecomastia
normal sex characters
Normal testes (volume and consistency) - no tumor
Lab tests

- no inflammatory parameters
- fasting glycaemia 93 mg/dl
- renal and hepatic functions: nl
- haematology nl

- *what else would you ask?*
Hormones:

- **free T4**: 1.2 ng/dl (0.8-2.0)
- **free T3**: 3.3 pg/ml (2.4-5.0)
- **TSH**: 0.7 µU/ml (0.2-3.5)
- **LH**: 5 mU/ml (2-15)
- **FSH**: 5.3 mU/ml (1.5-9.5)
- **total testo**: 5.2 nM (13-35)
- **free testo**: 0.120 nM (0.2-0.6)
- **estradiol**: 26 pg/ml (18-50)
- **prolactin**: 88 ng/ml 79 ng/ml (3-20)
Markers of testicular cancer:

- HCG normal
- alpha-foeto-protein normal
• Echo-mammography: confirms true gynaecomastia (≠ adipomastia)

• echography of the testes: normal

• pituitary MRI
Is it a prolactinoma?

Or another pituitary tumor with stalk compression?
Pituitary adenoma ≥ 10mm + PRL concentration < 200 µg/L

- low secreting PRL tumour (necrotic, haemorrhagic or cystic PRLoma, acromegaly with mixed GH-PRL adenoma,...)

- non-functioning pituitary adenoma and pituitary stalk compression responsible for hyperprolactinaemia

✓ cut-off? PRL < 160 µg/L if stalk effect


✓ TRH test? Not sensitive and specific!

✓ treatment trial with a DA for 3 months
### Endocrine test: TRH

<table>
<thead>
<tr>
<th>Temps (min.)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (µU/ml)</td>
<td>1</td>
<td>4.9</td>
<td>3.2</td>
<td>2.5</td>
<td>1.6</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>74.2</td>
<td>73.2</td>
<td>67.1</td>
<td>71.6</td>
<td>70.2</td>
</tr>
<tr>
<td>GH (ng/ml)</td>
<td>0.6</td>
<td>0.6</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

IGF-I *nl*

→ No acromegaly
Treatment

Treatment with cabergoline (sostilar) was started 1 tablet 0.5 mg 2x/week

After 2 months: libido and sexual function ↑

PRL 1.4 ng/ml
total testo 11.8 nM (13-35)
free testo 0.22 nM (0.2-0.6)
Evolution

• after 1 year gynaecomastia has resolved

• PRL 0.5 ng/ml
  free testo 13.2 nM (13-35)

IRM: further regression of the tumor
Diagnosis of microprolactinomas

When PRL < 200 µg/L + microadenoma at MRI,

- hyperprolactinaemia should be confirmed
- other causes should be excluded!

1) Hypothalamic or stalk lesions (radiotherapy, infiltration..)
2) Primary hypothyroidism (↑ TRH)
3) Renal failure
4) Polycystic ovary syndrome (continuous estrogens)
5) Drugs +++
6) Macroprolactinemia
Many drugs can cause hyperprolactinaemia!

- **Typical/atypical neuroleptics and antidepressants**
  - risperidone > olanzapine > quétiapine >> aripiprazole
  - Risperdal® Zyprexa® Seroquel® Abilify®
  - > 80% 35% 20% 0%

- SSRI and new IMAO

- **Gastrointestinal drugs**
  - antiemetics, anti-H2, proton pump inhibitors

- **Antihypertensive drugs**
  - some calcium antagonists (Lodixal®) and α-méthylldopa

- **Estrogens, opiates, protease inhibitors,**...
Macroprolactinemia should be ruled out...

- when [PRL] are below 250 µg/L,
- especially when typical symptoms are lacking
  (but galactorrhea in 20%, oligo/amenorrhea in 40%, pit adenoma in 20%)

= artefactually high PRL due to large MW complexes of multimeric PRL ↔ IgG or covalent bridges

recognized in all PRL assays but at a variable degree may be present in 15-40% of sera!
Case # 2

25 year-old man

presents with bilateral gynaecomastia
Medical History

- induction of puberty
Current problems

Since ± 10 years
slow-onset gynaecomastia
bilateral, L = R
not painful
libido and erectile function considered normal
Clinical examination

79.6 kg  1.86 m  BMI 23 waist 95 cm  
BP 12/6   HR 80/min

general examination normal

bilateral gynaecomastia

poorly developed sex characters 
small testes (4 ml)
Hormones

- free T4: 1.1 ng/dl (0.8-2.0)
- free T3: 3.0 pg/ml (2.4-5.0)
- TSH: 1.3 µU/ml (0.2-3.5)

- LH: 29 mU/ml (2-15)
- FSH: 47 mU/ml (1.5-9.5)
- total testo: 12.7 nM (13-35)
- free testo: 0.22 nM (0.2-0.6)

- estradiol: 30 pg/ml (18-50)

- prolactin: 18 ng/ml (3-20)
What is your first diagnosis?

Which test(s)?
• echography of the testes: small testes (20x10 mm) with heterogeneous content, very small nodules evoking Leydig cell hyperplasia

• caryotype: 47, XXY

• Diagnosis: *Klinefelter's Syndrome*
R/ testosterone injections 250 mg / 3 weeks and Andractim gel (dihydrotestosterone) locally
Case # 3

22 year-old man

presents with recent onset, painful
gynaecomastia
Medical History

- surgery for cholesteatoma
- no medical treatment

Familial History

- seminoma in the father
Current problem

Since ± 1 month
bilateral gynaecomastia
L = R
painful
libido and erectile function considered normal
Clinical examination

general examination normal

bilateral gynaecomastia

normal sex characters
normal testes at palpation!
Lab and hormones:

- free T4: 1.4 ng/dl (0.8-2.0)
- TSH: 0.8 µU/ml (0.2-3.5)

usual lab normal
# Lab and hormones:

<table>
<thead>
<tr>
<th></th>
<th>07/12</th>
<th>23/12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (total)</td>
<td>1174 ng/dl (400-1000)</td>
<td>31.1 nmol/l (12-35)</td>
</tr>
<tr>
<td>Testosterone (free)</td>
<td>30 ng/dl (6-25)</td>
<td>0.65 nmol/l (0.2-0.6)</td>
</tr>
<tr>
<td>Estradiol</td>
<td>80 pg/ml (10-30)</td>
<td>109 pg/ml (&lt; 35)</td>
</tr>
<tr>
<td>Estrone</td>
<td>97 pg/ml (10-60)</td>
<td>55 pg/ml (15-45)</td>
</tr>
<tr>
<td>LH</td>
<td>&lt; 0.1 U/l (1-10)</td>
<td>&lt; 0.1 U/l (2-15)</td>
</tr>
<tr>
<td>FSH</td>
<td>&lt; 0.3 U/l (1.5-8)</td>
<td>&lt; 0.1 U/l (1.5-9.5)</td>
</tr>
<tr>
<td>PRL</td>
<td>17 ng/ml (2-18)</td>
<td>20.5 ng/ml (3-20)</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>ND</td>
<td>10.9 µmol/l (2.5-12)</td>
</tr>
<tr>
<td>17OH-progesterone</td>
<td>ND</td>
<td>21.6 nmol/l (&lt; 5)</td>
</tr>
<tr>
<td>HCG</td>
<td>ND</td>
<td>0.03 U/l (&lt; 0.05)</td>
</tr>
<tr>
<td>Alpha-foeto-protein</td>
<td>ND</td>
<td>2.5 ng/ml (&lt;10)</td>
</tr>
</tbody>
</table>
Next steps ?
Testicular echography
Abdominal CT: normal

Diagnosis: left testicular tumor + secretion of estrogens

Differential diagnosis?
**Differential diagnosis**

1) **direct secretion of estrogens by the tumor**
   = « Sex-cord stromal tumors » (SCSTs) : <5% of testicular tumors (*leydigoma, …*)
   - 10% are malignant
   - intratumoral **aromatase** +++ oestradiol (et pfs oestrone) ↗ - LH et FSH ↘
   testostérone ↘ ou nle SHBG souvent ↗ - 17OHP, DHEA : nl

2) **secretion of hCG by the tumor** which stimulates local production of testosterone + and estrogens +++ by the Leydig cells
   = « Germ cell tumors » (GCTs) - generally malignant
   - Pure seminomas with syncytiotrophoblasts
   - Choriocarcinomas
   - Mixed tumors (seminomas + component of choriocarcinoma)
Orchidectomy: Seminoma
Orchidectomy: **Seminoma**

Immuno (+) for Placental-Like-Alkaline-Phosphatase (PLAP) = **Séminoma**
Orchidectomy: Seminoma

Syncytiotrophoblasts (+) for HCG
Orchidectomy: Seminoma

Leydig cell hyperplasia
Differential Diagnosis of Gynaecomastia
Differential Diagnosis of Gynaecomastia

- **true gynaecomastia**
  = benign proliferation of glandular ductal epithelium

- **pseudo-gynecomastia**
  = fat accumulation

- **mixed gynaecomastia**

- **other**
  - breast carcinoma, lipoma, hematoma, dermoid cyst, …
Physiological Gynecomastia

1. Newborn
2. Puberty
3. Old Age
Pathological Gynecomastia

1. estrogen excess or androgen shortage
   (↑ estrogen / androgen serum ratio)
2. abnormal tissue sensitivity for oestrogens or androgens
   (↑ oestrogen / androgen tissue ratio)
3. excess local conversion of androgens to oestrogens
   (↑ aromatase activity)

1. primary androgen deficiency
2. secondary androgen deficiency
3. increased testicular oestrogen production
4. increased extra-glandular oestrogen
5. medications
6. “idiopathic”
Primary Androgen Deficiency

- congenital: *Klinefelter - anorchia* ....
- androgen resistance: *testicular feminisation*
- defect in testosterone synthesis
- bilateral testicular lesion: *mumps - trauma - RXT - alcoholism*...
Secondary Androgen Deficiency

- congenital: *Kallmann* ....
- pituitary insufficiency: *adenoma - prolactinoma - trauma* ...
- hypothalamic insufficiency, chronic diseases, malnutrition
Increased testicular estrogen secretion

- hCG secretion: choriocarcinoma testis, bronchus ...
- estradiol secretion: Leydig cell tumour
- aromatase secretion: Sertoli cell tumour
Increased extra-glandular estrogens

- Hyperthyroidism: ↑aromatisation + ↑SHBG
- Cirrhosis: ↑aromatisation + ↑SHBG
- Secreting adrenal tumour: ↑DHEAS + ↑17-OHP
- Misuse of androgens / anabolic medications
Drug-induced Gynecomastia

- inhibition of testosterone activity
  - spironolactone
  - anti-androgens (cyproterone, flutamide, ...)
  - PPI (cimetidine, ranitidine, omeprazole)
  - antimitotics
  - imidazole (ketoconazole)

- direct or indirect oestrogen effect
  - treatment of gender dysphoria
  - gonadotrophins, hCG, clomiphene
  - digitalis

- unknown (case reports)
  - calcium-channel antagonists + ACE inhibitors + methyl-dopa
  - dopamine antagonists (phenothiazide, metoclopramide)
  - drugs (marijuana, heroine, methadone, amphetamines)
Idiopathic Gynecomastia

- More frequent in obesity
- Congenital

Androstenedione $\rightarrow$ Testosterone

$\uparrow$ Aromatase?

$\uparrow$ Oestrone $\rightarrow$ $\uparrow$ Oestradiol
Etiology of Pathological Gynecomastia

- Idiopathic
- Persistent pubertal
- Medication
- Cirrhosis
- Primary hypogonadism
- Testis tumour
- Secondary hypogonadism
- Hyperthyroid
- Other
Treatment of Gynaecomastia
Therapy depends upon underlying cause and severity of gynaecomastia

- **Idiopathic or pubertal gynecomastia**

  1. **Limited disease, few symptoms**
     - WATCHFUL WAITING: spontaneous improvement in majority of cases

  2. **Painful, large or persistent gynecomastia**
     - THERAPY NECESSARY (see further)
Therapy depends upon underlying cause and severity of gynecomastia

• Gynecomastia with underlying cause

  1. **Cause can be treated** (elimination of responsible medication, resection of tumor, …)
     • WATCHFUL WAITING after elimination of cause usually enough

  2. **Cause cannot be corrected** (e.g. idiopathic..)
     • THERAPY NECESSARY (see further)
Medical therapy

• I. Androgens

• DIHYDROTESTOSTERONE (gel, 5 g/day on chest)
  – 75% improvement, 25% complete disappearance
  – Side effects: limited
Medical therapy

• II. Anti-oestrogens

  - TAMOXIFEN (oral, 20 mg/day)
    • 50-80 % improvement, 10 % complete disappearance
    • 40 % not satisfied, wants surgery
    • Side effects : nausea, epigastric discomfort (limited)
Medical therapy

- **III. Aromatase-inhibitors**

  - **ANASTROZOLE** (oral, 1 mg/day)
    - Not more effective than placebo in puberty
    - Side effects: limited
    - Effective when aromatase is increased: Peutz-Jeghers syndrome with Sertoli cell dysfunction; familial gynecomastia; testosterone induced gynecomastia
Surgery

IV Plastic surgery

- Types
  - Subcutaneous mammectomy
  - Liposuction
  - Extensive surgery

- Side effects
  - Hematoma, seroma
  - Numbness of nipple
  - Irregularity of contour
  - Necrosis