Case Approach in Oncology & Paraneoplastic Syndrome

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Common cases you should know

- Lung cancer (NSCLC, SCLC)
- Germ cell tumor
- Unknown primary carcinoma

แต่ผู้ป่วยที่นำมาสอบมักไม่ตรงไปตรงมาเสมอ

มี complication จากโรคที่ต้อง approach ให้ได้

- Cord compression, SVC obstruction, leptomeningeal carcinomatosis
- Paraneoplastic manifestation/ genetic syndrome that will lead to diagnosis of cancer

อาจมีมากกว่าหนึ่งโรค (มะเร็ง + อื่นๆ)

อย่ากังวลเรื่องยารักษามะเร็งมากนัก เน้นการ approach มากกว่ารู้ basic principle ก็พอ ถ้าตอบได้ลึกเป็น bonus
Paraneoplastic Syndrome

**Definition**: disorder occurring at sites remote from the primary tumor and its metastasis

- Excessive production of substances (hormones)
- Host response to tumor (immune-process)

Appears in 10-15% of cancer patients, May be the first manifestation of an occult cancer

- Some are specific for particular tumor types
  - LEMS, SIADH
- Some occur with many tumor types
  - HCM, DIC, cachexia

Not all syndrome parallels the underlying malignancy

- Yes ➔ Endocrinologic
- Unpredictable ➔ Immune/neurologic
หญิง 64 ปี heavy smoker, HTN, DLP

กย. 57 ไวกินยาร์ ไม่มีเลือดปน น้ำหนักลด
CXR มีก้อนในปอด

พย. 57 เหนื่อยมากขึ้น ส่งปรึกษาทำ bronchoscopy
review system พบว่ามีซางข่อนแรง ลูกจากโคลนสั้นสีกระจ่าง
ขื่น หวิ่นละได้ไม่ช้า ไม่ปวดหลัง/ปวดหัว กลิ่นอุจจาระปัสสาวะได้
<table>
<thead>
<tr>
<th></th>
<th>Rt.</th>
<th>Lt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>deltoid gr.</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>bicep / tricep</td>
<td>IV / IV</td>
<td>IV / IV</td>
</tr>
<tr>
<td>wrist F/E</td>
<td>IV+</td>
<td>IV+</td>
</tr>
<tr>
<td>finger F/E</td>
<td>IV+</td>
<td>IV+</td>
</tr>
<tr>
<td>hand grip</td>
<td>IV+</td>
<td>IV+</td>
</tr>
<tr>
<td>hip F/E</td>
<td>III+ / IV</td>
<td>III+ / IV</td>
</tr>
<tr>
<td>knee F/E</td>
<td>IV / IV</td>
<td>IV / IV</td>
</tr>
<tr>
<td>ankle dorsiflex</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>plantarflex</td>
<td>V</td>
<td>V</td>
</tr>
</tbody>
</table>

**Tone**: normal  
**Sensory**: normal  
**CN**: ptosis gr I  
**DTR**:  
**BBK**: plantar response
Imp : Proximal muscle weakness
- Hyporeflexia, mild ptosis

DDx :

What else you want to look for in history, exam and initial labs?
Additional information

- Disability improves and worsens intermittently
- Enhanced ptosis +ve,
- Knee jerk reflex 3+ after sustained contraction
- Na 136, K 4
- Normal TFT, CK

**Diagnosis**: Lambert-Eaton myasthenic syndrome

**Pathology** from bronchoscope: small round cell tumor
Proximal Muscle Weakness and Cancer

- LEMS : Small cell lung cancer
  - Many interesting paraneoplastic syndrome

- MG : thymoma

- Dermatomyositis
  - Lung, GI (gastric/colon), ovary, NPC

- Cushing syndrome : ectopic ACTH
  - SCLC, Neuroendocrine tumor : thymic/ bronchial carcinoid, pancreatic NET
Lambert-Eaton Myasthenia Syndrome

- Paraneoplastic in 50-60% → Small cell CA (but only 5% of SCLC have LEMS)
- **Clinical point**: decreased DTR which improves after repetitive movement
- Can be associated with autonomic disturbance: impotence, dry mouth, constipation, abnormal sweating
- Occ. with CN signs: ptosis, diplopia, dysarthria (less common than MG)
- **Electrodiagnostic**: Decrement of action potential with low frequency stimulation, increment w/ high frequency stimulation.
Lambert-Eaton Myasthenia Syndrome

- Antibody against P/Q type voltage gated Ca channel (VGCC) (pre-synaptic) → prevent entry of calcium into the cell (necessary for release of Ach)
- Diagnostic for paraneoplastic LEMS
- Usually respond to Rx of cancer
- Respond well to IVIG or plasma exchange or immunosuppression
Myasthenia Gravis

- Paraneoplastic in 10-15% of cases

- **Thymoma**: other paraneoplastic syndrome
  - PRCA, pernicious anemia, nephrotic syndrome, thyroiditis, hypogammaglobulinemia

- **CN involvement more common than in LEMS** (ptosis, bulbar)

- **EMG**: decremental compound muscle action potential w/ repetitive stimulation → then stabilizes or increasing afterwards
Myasthenia Gravis

- Anti-AchR +/- other muscle protein Ab,
  - Not diagnostic for paraneoplastic disease

- Thymoma with MG: Better outcome c/w those without MG

- MG activity not always correlate with thymoma status

- Rx: thymectomy, +/- immunomodulatory Rx
  - chemoRx in metastatic disease
Neurologic Paraneoplastic Syndrome

- Relatively rare, 1% of cancer patients
- Most are immune-mediated (autoimmune)
- Antigens common to the tumors and nerve cells

- Usually *precedes* the identification of cancer (2/3)... most CA are found within 1 year

- Common cancer with neurologic paraneoplastic syndrome
  - Small cell lung cancer > NSCLC
  - Breast cancer, ovarian cancer
  - Lymphoma

- Most follow a subacute course, progressing over several weeks- months and then stabilizing

- Most neurologic syndrome *do not* parallels cancer response
Neurologic Paraneoplastic Syndrome

**PNS involvement**
- More common than CNS involvement
- Ex. MG, LEMS, AIDP
- Could be responsive to immunomodulatory Rx: LEMS, AIDP

**CNS involvement**
- Subacute progression over weeks to months
- Can render a previously fit patient bedbound
- Usually resistant to immunomodulatory Rx
- Prognosis is poor
- Ex: cerebellar degeneration, limbic encephalitis, opsoclonus-myoclonus
- CSF: inflammatory (pleocytosis, high protein) → decline with time
- Brain imaging: usually unremarkable except limbic encephalitis
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>% Paraneoplastic</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEMS</td>
<td>60%</td>
<td>Small cell lung CA</td>
</tr>
<tr>
<td>MG</td>
<td>15%</td>
<td>thymoma</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>20%</td>
<td>NHL, ovary, lung, NPC</td>
</tr>
<tr>
<td>Sub acute sensory neuropathy</td>
<td>20%</td>
<td>Lung, lymphoma, MM</td>
</tr>
<tr>
<td>Limbic encephalopathy</td>
<td>50%</td>
<td>SCLC, germ cell, breast</td>
</tr>
<tr>
<td>Subacute cerebellar degeneration</td>
<td>50%</td>
<td>Ovary, breast, small cell, Hodgkin's</td>
</tr>
<tr>
<td>Opsoclonus-myoclonus</td>
<td>40%</td>
<td>Neuroblastoma, breast, SCLC</td>
</tr>
</tbody>
</table>
Dermatomyositis

- Proximal muscle weakness
- Heliotrope: violaceous color of the eyelids, often with edema
- Gottron’s papule: keratotic papules over knuckles
- Widespread erythema, often over the elbows and knees, resembling psoriasis
- Photosensitivity
- Nail cuticle abnormalities, including telangiectases, thickening, roughness, overgrowth, and irregularity.
Dermatomyositis/ Polymyositis

- About 20-25% have internal malignancy esp. > 50 years old
  - 5-7–fold increase risk compared to general population
  - Excess risk declines with time with peak incidence in first 2 years
- Risk is higher in dermatomyositis (32% w/ CA vs 15% in PMS)
- Common autoAg in tumor and muscle cells
- **Associated CA**: ovary, breast, lung, pancreas, lymphoma, other GI (stomach, colon), bladder
  - Asian: NPC
- May occur before, at Dx or after Dx of cancer
- Very high CK
Dermatomyositis/ Polymyositis

Should cancer be searched for?

- **Extensive blind** evaluation of patients with dermatomyositis is **not** warranted.

- **Extent of w/u for CA**: depends on age and symptoms
  - detailed PE, breast, pelvic, PR
  - Routine labs: CBC, chem., UA, CXR, FOBT
  - **Age-appropriate cancer screening**: MMG, PV, colonoscopy
  - If symptomatic (wt loss, anorexia, localizing symptoms) → CT chest / abdomen has higher yield than tumor markers
  - Tumor markers: no real use..? CA125, PSA, CA19-9
    - Higher OR of cancer with elevated baseline value
    - Continued periodic screening for up to 4 years

- **Some improve w/ Rx of CA, but usually immuno Rx needed**
  - Prednisone, azathioprine, MTX → most do not recover completely
# Results of Non-routine Screening Tests in Pts with DM/PM

<table>
<thead>
<tr>
<th>Test</th>
<th>No. Performed</th>
<th>Directed by an abnormal findings</th>
<th>Positive Results in “blind” subgroup</th>
<th>Average positive result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT scan</td>
<td>24</td>
<td>6 / 6 (100%)</td>
<td>5 / 18 (28%)</td>
<td>11 / 24 (46%)</td>
</tr>
<tr>
<td>PET</td>
<td>28</td>
<td>2 / 8 (25%)</td>
<td>1 / 20 (5%)</td>
<td>3 / 28 (10%)</td>
</tr>
<tr>
<td>Colonoscope</td>
<td>16</td>
<td>1 / 3 (33%)</td>
<td>1 / 13 (8%)</td>
<td>2 / 16 (13%)</td>
</tr>
<tr>
<td>Small bowel XR</td>
<td>9</td>
<td>0 / 1</td>
<td>0 / 8</td>
<td>0</td>
</tr>
<tr>
<td>Thyroid image</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MRI</td>
<td>3</td>
<td>1 / 2 (50%)</td>
<td>1 / 1 (100%)</td>
<td>2 / 3 (67%)</td>
</tr>
<tr>
<td>Tumor markers</td>
<td>20</td>
<td>0 / 1 (0)</td>
<td>3 / 19 (16%)</td>
<td>3 / 20 (15%)</td>
</tr>
<tr>
<td>BM Bx</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other Bx</td>
<td>12</td>
<td>9 / 12 (75%)</td>
<td>0 / 0</td>
<td>9 / 12 (75%)</td>
</tr>
</tbody>
</table>

ชาย 51 ปีพนักงานธนาคาร ปริญญาตรี

- CC: จำ process การทำงานไม่ได้ 1 wk PTA
- 1 wk PTA ตื่นเส้าไปทำงานตามปกติ จะเริ่มทำงานแล้วการระบบการทำงานไม่ได้ จ้าขั้นตอนการจ่ายเงินให้พนักงานไม่ได้ ต้องหยิบเอกสารเก่าขึ้นมาดูแล้วพอได้ก็ค่อยๆทำไปจนจบได้ เดินทางกลับบ้านโดยรถไฟฟ้า BTS ได้ ทำกิจวัตรประจำวันอีก ได้ตามปกติ
- ปกติเคยไปบ้านน้องสาวหลายครั้งแต่ตอนนี้นึกรายละเอียดในบ้านไม่ออก
- ไม่มีไข้ ไม่มีปวดศีรษะ ไม่มีผื่นตามตัว ไม่มีอ่อนแรง/ชา ไม่มีหูแหวนหรือเห็นภาพ หลอน

- PH: สูบบุหรี่ 20 บุหรี่/วัน x 20+ yrs
  alcohol 1-2 bottles/wk, no drugs abuse
- HT ไม่ได้กินยาประจำ
ชาย 51 ปี หน้ากงานธนาคาร ปริญญาตรี

- PE : unremarkable
- Neuro : alert, orientation √
  - MMSE : 29/30
  - Impaired executive function
Clinical:
- Short-term memory deficit (80%) with intact cognitive function.
- +/- partial complex seizure (50%),
- confusion (40%), psychiatric symptoms (40%)

40% may occur AFTER cancer diagnosis

One of a few that brain image helps: abnormal signal in hippocampus

DDx: herpes encephalitis, other autoimmune limbic encephalitis

CA: Small cell lung cancer, testicular CA, breast CA

Ab: Anti-Hu, Anti-Ma1-2, Anti CV2, Anti NMDA, Anti AMPA

Occasionally improved with Rx of primary CA
Paraneoplastic Cerebellar Degeneration

- Acute or subacute, pancerebellar syndrome, usually symmetrical:
  - gait, dysarthria, dysphagia, tremor, N/V, eye movement abnormalities (nystagmus, diplopia), vertigo

- Results in severe disability (50-80% bedridden)

- Immune-mediated destruction of Purkinje cells

- Most precede CA, but 30% may occur AFTER cancer diagnosis

- MRI: normal or atrophic cerebellar (late)

- DDx: drugs (Dilantin, ARA-C), alcohol, prion dz, MS, ADEM

- Most common asso. CA are
  - Breast CA, ovary (anti-Yo, Ri)
  - small cell lung CA (Anti-Hu)
  - Hodgkin’s disease (Anti-Tr, Anti-mGluR)

- Rarely respond to Rx of cancer
Small Cell Lung Cancer

- Smoking related disease
- Rapid tumor growth, more aggressive clinical course than NSCLC: don’t wait too long to refer!!
- Most are central in location
- Almost always a systemic disease → 2/3 have metastasis @ Dx
- Several paraneoplastic manifestations
  - SIADH
  - Cushing’s syndrome: Ectopic ACTH
  - Lambert-Eaton myasthenia
  - Cerebellar degeneration, Limbic encephalitis
  - Vision loss: Anti recoverin
- Sites of metastasis:
  - LN, liver, bone, bone marrow, brain
Staging of SCLC

- Does not use TNM → not a surgical disease (No role of surgery in general)

- staging based on anatomy

1. **Limited stage**: lesions confined within one hemothorax, one port of RT possible
2. **Extensive stage**: multiple sites (pleural effusion, distant organ)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Untreated</th>
<th>Survival Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited 30-40%</td>
<td>12 wks</td>
<td>12-20 mos</td>
</tr>
<tr>
<td>Extensive</td>
<td>5-6 wks</td>
<td>7-11 mos</td>
</tr>
</tbody>
</table>
# Treatment of SCLC

- Chemosensitive, radiosensitive
- but recurrence rate is high even in early stage

## Limited disease
- ChemoRx + radiation
- Cisplatin or carboplatin + VP16
- Response > 70%
- If no residual dz → prophylactic brain RT improves survival
- 2 yr-survival 15-40%

## Extensive disease
- ChemoRx alone (RT optional)
- Cis/carbo + VP16
- Response 50%
- 2 yr survival : rare
- Median survival 6-8 months
Histologic Classification of Lung Cancer

- Adenocarcinoma
- Squamous cell carcinoma
- Large cell carcinoma
- Small cell carcinoma
Advance Non Small Cell Lung CA
A Shift in Concept

**Past**
- Histology doesn’t matter
  - Same Rx
  - Same prognosis

**Present**
- Histology matter
  - Molecular classification
  - Prognosis varies depends on subtype
  - Rx adapted according to histology/molecular profile
Molecular alterations in lung cancer

**US**
Adenocarcinoma

- No oncogenic driver detected: 36%
- Mut >1 gene: 3%
- MET 1%
- NRAS 1%
- MEK1 <1%
- ALK 8%
- PIK3CA 1%
- BRAF 2%
- KRAS 25%
- EGFR (other): 4%
- HER2: 3%

(East Asia)

- Adenocarcinoma, never smokers

- UKN/other: 9.6%
- ALK 5.8%
- KRAS 1.9%
- HER2 3.8%
- EGFR 78.8%

(n=52)

**US Adenocarcinoma**

(n=733)

- Squamous cell CA: Molecular characteristic less well-defined than adenoCA

Johnson, et al. ASCO 2013
EGFR (Epidermal growth factor receptor)

- Mutations in EGFR cause uncontrolled cell growth (driver mutation)
- Clinical features suggestive of EGFR mutation (not absolute)
  - adenoCA in female, Asian decent, non-smoker
Treatment of Advanced NSCLC (Metastasis & Malig. Effusion)

- All patients: Supportive Rx (symptomatic Rx)
  - Medications
  - Local RT: bone / brain mets / airway obstruction
  - Intervention: chest drain, airway stent, etc

- Cancer-specific Rx:
  1. ChemoRx: any histology
     - some patients, good status ECOG 0-2
     - Platinum-doublet regimen: carboplatin/cisplatin + any agents (paclitaxel, docetaxel, gemcitabine, VP-16, pemetrexed)
     - Response rate 20-40%
     - Improvement in survival, symptom and quality of life of patients treated with chemotherapy compared to no Rx
  2. Molecular targeted Rx:
     - EGFR inhibitor in mutation +ve cases (preferred)
     - ALK inhibitor if ALK+ve
  3. ImmunoRx - 1-y survival 30-40%
Molecular targeted therapy: it is making a difference

- BSC: 2–5 months
- Single-agent platinum: 6–8 months
- Platinum-doublets: 8–10 months
- Targeted therapies: >18 months

Line of Palliative Systemic Rx
unknown EGFR mutation status

First line:
• Combination chemotherapy (platinum-based)
• single agent chemoRx (if elderly or borderline performance status)
X 4-6 cycles

progression

Second-line:
• Single agent chemoRx : docetaxel, pemetrexed
• EGFR TKI* (adenocA) : erlotinib, Gefitinib

progression

Third-line:
• EGFR TKI*: erlotinib, Gefitinib

* EGFR/ALK should be tested if possible
Line of Palliative Systemic Rx
Known Molecular Status

Squamous cell CA

1st
Platinum-doublets
X 4-6 cycles

2nd—3rd
Docetaxel, or
EGFR inh. if Tested +ve (rare)

Platinum-doublets
X 4-6 cycles

adenoCA

EGFR/ALK wildtype
Platinum-doublets

EGFR/ALK mutation
Platinum-doublets
OR EGFR/ALK inhibitors

Docetaxel, or Pemetrexed

• Platinum-doublets,
• EGFR/ALK inh (if not given in 1st line)
• Docetaxel, or
• Pemetrexed
NSCLC Treated with TKI

EGFR exon 19 mutation
High response rate (60-80% in mutation +ve tumor)

Benefit regardless of which line of Rx given: can be used in 1\textsuperscript{st} (mutation +ve only), 2\textsuperscript{nd} or 3\textsuperscript{rd} line of Rx

Side effects: skin rash, mucositis, diarrhea, dry skin, interstitial lung disease

Lopes et al. WCLC 2013. Abs P2.11-015.
skin rash of EGFR inhibitors
Case Presentation – The First ALK-Positive Patient Treated with Crizotinib

Pre-Treatment

Crizotinib x 12 weeks
The Importance of Molecular Testing

- **EGFR mutation**: Erlotinib or gefitinib
- **ALK (or ROS1)**: Crizotinib, other ALK TKIs
- **RET**: Cabozantinib, vandetanib, ponatinib, other RET TKIs
- **Oncogenic Driver X**

**NSCLC**
45 yo male, pain in right shoulder for months, unrelated to activity

Now noted numbness in right hand and weight loss

Not related to neck movement
What do you see ???
Superior Sulcus Tumor (Pancoast’s Tumor)

- Referred pain to scapula and shoulder
- Pain in C₈-T₁ distribution → shoulder-arm medially (lower brachial plexus)
  - Weakness & atrophy of hand muscles
  - Thenar m, impairment of adduct/abduct
  - Hypothenar
- Horner’s syndrome → sympathetic chain/stellate gg.

- Respiratory symptoms not common (peripheral location of tumor)
- Look for other clinical signs of distant mets
  - Bone pain, liver mets, brain mets
FIGURE 4
The red structure indicates a Pancoast tumor. The inset indicates the location of the tumor.
Treatment of Locally Advance NSCLC (Disease confined to thorax, no distant metastasis)

- Mediastinal LN/SPC involvement, invasion into mediastinal structure including SVC syndrome, invasion of vertebra/nerves
- Most patients die from distant metastasis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation alone</td>
<td>8-9</td>
</tr>
<tr>
<td>Sequential chemoRx and radiation</td>
<td>12-14</td>
</tr>
<tr>
<td>Concurrent chemoRx and radiation</td>
<td>17-19</td>
</tr>
</tbody>
</table>

- Esophagitis is the main side effects
- Pancoast tumor: if responds well to CCRT → resectable → improves outcome
- Role of targeted drug in this stage is not clear yet
What is the diagnosis?
Hypertrophic Osteoarthropathy (HOA)

- Abnormal proliferation of skin and osseus tissue at distal limb
- Digital clubbing
- Oligoarthritis, symmetrical: knee, ankle

- Periostosis of tubular/long bones: painful aching of distal extremities (wrist, knee, ankle), usu symmetrical, gravity dependent
  - Detected by long bone film & bone scan

- Secondary HOA more common
  - Strong association with various lung and pleural malignancies and diseases
  - May precede the diagnosis of CA
HPOA: Cortical uptake along bony shaft seen in bone scan
Periosteal reaction of tubular bone: diaphysis/metaphysis
Primary HPOA

- Rare, autosomal dominant
- Skin change: pachydermia: oily, thickened, elephant-like skin
- Abnormal PGE2 met.

Secondary HPOA

- Lung cancer
  - adenoCA>> small cell
- Pulmonary/mediastinal metastasis
- Lung infection
- Right to left shunt
- Misc: cirrhosis, GI inflammation
- Improve with successful Rx of CA
- Symptomatic Rx: NSAIDs
ชาย อายุ 31 นักธุรกิจ

6 เดือนก่อน พฤติกรรมก้าวร้าวขึ้น ทำร้ายลูกน้อง

flights of idea

ญาติสังเกตว่าอ้วนขึ้น สิวขึ้น ผิวคล้ำลง ดูลุกจากเก้าอี้ ลำบาก

ตรวจพบ HbA1C 9.2, BP สูง → insulin

ระยะหลังเริ่มมี hallucination

PE : acne @ chest, purplish striae,
hyperpigmented inner lips, areolar proximal muscle weakness

K 2.1, HCO₃ 36, FBS 245
Ectopic ACTH Syndrome
Clinical Presentation

- Cushinoid features
- Muscle wasting
- Hypokalemia with metabolic alkalosis, hyperglycemia
- HTN
- Hyperpigmentation (ACTH, MSH)
- Less prominent: wt loss, centripetal fat distribution

Cushinoid features are usually less prominent than that seen in Cushing’s disease due to shorter time of exposure to cortisol (aggressive nature of the tumor → SCLC)
Ectopic ACTH Syndrome

- Most are associated with
  - lung cancer (50%): small cell > NSCLC
  - Pancreatic neuroendocrine tumor
  - Thymic carcinoid / bronchial carcinoid
Ectopic ACTH Syndrome: Investigation

Confirmation of excess ACTH

- Urine free cortisol levels fluctuate but are typically greater than 2 to 4 times normal
- Plasma ACTH level is usually >200 pg/mL
- No suppression by high dose dexta (in contrast to ACTH-producing pituitary tumor).... But overlaps do occur → not definitive

Seeking the etiology

- Majority have primary lung/thymic tumor → CXR, CT chest
  - If negative: think of pancreatic neuroendocrine tumor → CT abdomen
Ectopic ACTH Syndrome: Prognosis

- Depends on tumor type and disease stage
  - Small cell lung CA: highly aggressive, most die within 1-2 years,
  - Carcinoid tumor: can be indolent
  - Pancreatic NET: can be indolent

- Shorter survival than those without Cushing (Higher incidence of infection)
Back to the Case

- 24 hr urine free cortisol = 6678 mcg
- ACTH level 281 pg/ml
- Low and high dose dexamethasone. → non-suppressible

- CT adrenal: bilat adrenal hyperplasia
- MRI brain: pituitary microadenoma
- BIPSS: no gradient of central and peripheral ACTH
Biopsy mass: neuroendocrine carcinoma

Sputum mAFB: nocardia
Ectopic ACTH: Treatment of Cancer

**Tumor Rx**
- Small cell lung CA
  - Cis or carboplatin + etoposide +/- RT
  - Rapid response
  - High risk of infection if hypercortisolism not controlled
- Carcinoid tumor/ pancreatic Neuroendocrine
  - Resection if feasible
  - Embolization of liver mets
  - chemoRx of limited use
  - targeted Rx: sunitinib, everolimus

**Rx of excess cortisol**
- Adrenalectomy
- Ketoconazole 400-1200 mg/d
  - Closely follow LFT
  - N/V/rash/diarrhea
- Aminogluthetimide/ metyrapone (not available in Thailand)
- Etomidate IV: IPD only
- Mitotane: adrenolytic (not available in Thailand)
ชายไทยคู่ อายุ 40 ปี

4 สัปดาห์ เหนื่อยมากขึ้นเมื่อออกแรง ไม่เจ็บหน้าอก ไม่ไอ ถ่ายปกติ แต่แน่นท้องหลังอาหาร

แขนขวาปวดบวม 2 สัปดาห์ ปฏิเสธการกระทบกระแทก/ อุบัติเหตุ หรือ การใช้งานผิดปกติ ไม่เคยเป็นมาก่อน

ไม่มีโรคประจำตัว ไม่สุบบุหรี ไม่มียาประจำ

ตรวจร่างกาย

PR 90, BP 130/60, RR 26, Moderate pallor, no jaundice

No adenopathy Heart : SEM gr 3/6

Lung : slight decreased BS BLL

Abdomen : mildly distended, no hepatomegaly, no ascites

Rt arm : swollen and tender
Doppler U/S: acute thrombosis of Rt. Jugular & subclavian V

Hct 31%, WBC 8300, Plt 575,000

Other labs: WNL except albumin 2.4

Stool occult blood: negative

CT chest & abdomen: focal gastric wall thickening, peritoneal seeding, small ascites, no pulmonary embolism

EGD: infiltrative lesion @ gastric body

Biopsy: diffuse poorly differentiated adenoCA
History: First Person to Describe Paraneoplastic Syndrome

- 1865: Dr. Armand Trousseau, professor of clinical medicine in Paris

- Phlegmasia alba dolens (painful white inflammation)

- Observation of correlation of visceral malignancy and migratory thrombophlebitis

- 2 years later he diagnosed himself with the syndrome → gastric CA
Trousseau’s Syndrome

- **Classic description**: recurrent, migratory thrombophlebitis involving the venous or arterial system

- **Spectrum of disorder**
  - Venous and arterial thrombosis (stroke, MI)
  - Marantic endocarditis (nonbacterial thrombotic endocarditis)
  - Chronic DIC

- most commonly seen in mucin-producing adenoCA of the GI tract (gastric, pancreatic, hepatobiliary)
  - Non-mucin producing: lymphoma, renal cell CA, GBM
  - Prostate CA, Ovarian cancer

- Mostly seen in advance stage cancer
Thrombosis in Malignancy

- **Hypercoagulable state** produced by malignant cells & their cytokines
  - Secretion of prothrombotic substances: tissue factor, mucin, cancer procoagulant? (direct factor X activation) → thrombin generation
  - Tumor damage to endothelial cells

- Anatomical factor: slow venous flow state from tumor bulk

- Treatment factor: surgery, drugs
  - Tamoxifen
  - Thalidomide, lenalidomide
  - Targeted drugs: VEGF inhibitors (bevacizimab, sorafenib, sunitinib)

- **Prognosis**: cancer pts with thrombosis have higher mortality compared to those without thrombosis
Should Cancer be Searched for in 1st Unprovoked DVT/Thrombosis?

- ~10% of unprovoked DVT cases will be Dx’ed w/ CA in the first 1-2 years (greatest risk in the first 6 months)

Limited vs extensive screening?

<table>
<thead>
<tr>
<th>Limited screening</th>
<th>Extensive screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>history, PE, PV/PR basic labs, CXR</td>
<td>Limited screening PLUS</td>
</tr>
<tr>
<td>Age-appropriate cancer screening</td>
<td>CT, tumor markers, endoscopy, PET scan (vary among studies)</td>
</tr>
</tbody>
</table>

- More cancers detected in extensive screen
- Survival not improved in most studies

Cancer and Thrombosis: Treatment

- **Rx**: Heparin
  - Anti-thrombin effect
  - Inhibition of selectins (carcinoma-mucin-dependent adhesion)
  - Induction of tissue factor pathway inhibitor

- Warfarin is less effective, yet better than no Rx
  - No difference in survival between heparin and warfarin

- DOACs are not recommended in cancer patients (prob. As effective as warfarin)

- Duration: life-long or at least 3-6 months
  - active cancer, prior VTE, residual VTE after 6 m (DACUS)
A 42-year-old female

Known case breast cancer stage 3, LN 15+ve

ER neg, PR neg, HER2 1+

Just completed adjuvant chemoRx 2 months ago

Presented with severe headache for 3 days and unsteadiness
Neuro exam

- Well oriented
- Papilledema bilat
- EOM full
- Mild Rt. facial palsy LMN
- Motor : UE normal tone/ strength
  - LE : flaccid tone, grade 4 weakness bilat
    - Absent DTR both knees / ankles
- Cerebellar : impaired FTN
- Sensory : decreases PPS L3-5,S1 & perianal sensation

Locate the lesion?

Investigation?
T1 post Gadolinium
Leptomeningeal Metastasis Diagnosis- MRI
Leptomeningeal Metastasis

- Solid or hematologic malignancy
- Etiology
  - Breast & NSCLC (adenocarcinoma) : most common
  - Melanoma in westerners
  - Lymphoma / leukemia
  - Others: gastric, ovarian, RCC, bladder CA, etc
- Dismal prognosis in general
  - 60-80% have progressive, refractory systemic disease at time of Dx
  - Untreated: survival 4-6 weeks
  - Treated: survival 12-16 weeks (may be longer in breast CA & lung CA with mEGFR)
Leptomeningeal Metastasis

Signs - symptoms

- Cerebral involvement / obstruction of CSF flow
  - Headache, memory loss, lethargy, seizure, behavioral changes, papilledema, gait disturbance

- CN involvement
  - Common: 3, 4, 6, 7, 8

- Spinal cord and roots
  - Nuchal rigidity, neck/back pain, incontinence
  - Weakness, sensory loss

- Clinical hallmarks is **multifocal neurological symptoms and signs**

- Imaging: linear and/or nodular enhancement of the leptomeninges, cranial nerves and spinal nerve roots, especially the cauda equine
  - Hydrocephalus +/-
Leptomeningeal Metastasis
CSF: Gold Standard

- OP increased in 50%
- Pleocytosis (L) 50%
  - Eosinophils in lymphoma
- Protein typically increased due to disruption of BBB
- Glucose < 40 (25-30%)
- MRI brain should be done before LP (co-existing brain mets)

**CSF cytology (10ml)**

- 1st LP 55%
- 2nd LP 80%
- Each subsequent LP (3-7) +2%
- Persistently negative: autopsy proven 20%
- Ventricular or cistern 5%
Standard Treatment

- **Intrathecal chemoRx**
  - MTX
  - Ara-C, liposomal ara-C, thiotepa, topotecan
  - Given 2-3 times/week x 3-4 weeks → weekly x 4, then monthly

- **Radiation**
  - Focal to sites of visible bulky dz and sites of CSF obstruction
  - Craniospinal area

- **Systemic chemoRx**: BBB problem
Carcinomatosis peritonii

- Ascites, palpable abdominal mass/omental cake, sister Mary Joseph nodule, clinically small bowel obstruction
- Mostly are adenocarcinoma

<table>
<thead>
<tr>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>55% Gyne</td>
<td>55% GI (incl. pancreas)</td>
</tr>
<tr>
<td>25% GI, hepatobiliary</td>
<td>25% GI</td>
</tr>
<tr>
<td>25% unknown, others (lung, breast)</td>
<td>25% GI, others (lung)</td>
</tr>
</tbody>
</table>

Morphology helps sometimes:

- Papillary adenoCA → ovarian CA in female, pancreatic/NSCLC possible
- Signet ring, poorly differentiated, mucin producing → favor GI tract primary (colorectal, gastric, cholangioCA / pancreatic CA)
Carcinomatosis Peritonii
Symptom-Directed Investigation

- **CT abdomen/pelvis**: look for primary, extent of abdominal mets
- **Endoscopy if**:
  - Fe-def. anemia, GI symptoms not explained by ascites (N/V/bowel habit change, etc)
  - Mucin producing adenoCA/signet ring
  - Abnormal findings in CT
  - Male
- **Tumor markers**: may not be very helpful or sometimes confusing, useful for follow-up Rx response
  - CA 125 (female): a marker for peritoneal disease (not just CA ovary) BUT high levels and adenoCA +/- pelvic mass is suggestive of ovarian in origin
  - CEA/CA19-9: very non specific, can be elevated in ovarian as well
- **Pathology review/special stain is vital**
  - GI tract marker: CK 20, CDX 1, etc
69 year-old female, non smoker
2-3 months: Abdominal discomfort, wt loss, back pain
PMH: HTN, breast surgery 5 years ago
PE:
- LN not palpable
- ascites, no hepatomegaly
- Decreased BS LLL
- Absence right breast

Lab: Hct 33%, normocytic, LFT/ Cr/ Ca normal, albumin 2.5
- Stool occult blood: negative
- CXR: left pleural effusion 1/3
- Abdominal paracentesis: adenoCA

CT whole abdomen: ascites, atrophic ovaries, no liver mets
Pelvic exam: atrophic vagina, normal pap
CA 125: 1200 (NI < 35)
Iron study: ACD
P-C

- abdominal pain
- describe findings
Pathologist’s Help

- Cells were not papillary-like, not signet ring cell
- Ask to send large amount ascites for cytospin/cell block
- ER positive
- Her 2 negative
- Tissue from prior breast CA: lobular carcinoma, ER/PR positive, Her2 negative
- Learning points:
  - Misleading CA125
  - Bone mets not common in ovarian CA
Treatment of Carcinomatosis Peritonii

**Known primary**: Rx per standard of each cancer

- **Colorectal**: 5FU +/- oxaliplatin or irinotecan
- **Gastric**: 5FU based
- **Breast ER+ve**: endocrine Rx / chemoRx,
  - HER2+ve: trastuzumab + chemoRx
  - triple negative: chemoRx
Treatment of Carcinomatosis Peritonii

**Unknown primary**: select chemoRx to treat the most responsive/treatable tumor

- In female: Rx as ovary $\rightarrow$ very Rx responsive
  - Platinum + taxane: survival 2 years, RR 40-60%
  - Surgery: TAH/BSO/omentumectomy if possible

- In male: use GI CA drug: mainly 5FU-based
# Summary of Drugs in Common Cancers

<table>
<thead>
<tr>
<th>cancer</th>
<th>Medical Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>1. Platinum-based regimen (cisplatin / carboplatin + paclitaxel, docetaxel, gemcitabine or premetrexed)</td>
</tr>
<tr>
<td></td>
<td>2. EGFR inhibitor : gefitinib, erlotinib</td>
</tr>
<tr>
<td>Breast CA</td>
<td>1 ER+ve : endocrine Rx (aromatase inhibitor, tamoxifen)</td>
</tr>
<tr>
<td></td>
<td>2. Her2+ve : trastuzumab + chemoRx (paclitaxel, docetaxel, capecitabine)</td>
</tr>
<tr>
<td></td>
<td>3. Triple negative: chemoRx single agent (paclitaxel, docetaxel, capecitabine)</td>
</tr>
<tr>
<td>Colorectum</td>
<td>5FU-based +/- bevacizumab or cetuximab (ex : FOLFOX, FOLFIRI, capecitabine)</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>BEP (bleomycin, etoposide, cisplatin)</td>
</tr>
<tr>
<td>Prostate CA</td>
<td>Androgen suppression (orchidectomy, LHRH agononist +/- antiandrogen)</td>
</tr>
<tr>
<td>cholangioCA</td>
<td>Gemcitabine +cisplatin</td>
</tr>
</tbody>
</table>
Thank You for Your Attention !!
Imp : Proximal muscle weakness

DDx :

- NMJ disorder, myositis
- Metabolic : thyroid, cushing, hypokalemia

What else you want to look for in history, exam and initial labs

- Fluctuation, other neuro deficit
- Drug list : lipid-lowering drugs, steroids
- Skin signs
- Appearance
- Symptoms of rheumatologic disorder
- Elyte, CPK, TFT, glucose
Mass at apical lung
Destruction of 2nd rib