Paraneoplastic Syndrome & New Cancer Treatment Related Complications for Internists

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**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 activity of underlying malignancy
  - Yes → Endocrinologic
  - Unpredictable → Immune/neurologic
Paraneoplastic Syndrome

- Neurological
- Endocrine
- Dermatological
- Renal
- Hemato.
- Others
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, thymoma
- In 20%→ no cancer is ever found → success of host immunologic response to control tumor growth ??
  - PET/CT increases the cancer diagnostic yield by 20% beyond CT chest/ abd
- Most follow a subacute course, progressing over several weeks- months and then stabilizing
- Most neurologic syndrome do not parallels cancer response
- These syndromes are often associated with serum or CSF positivity of onconeuronal or neuronal cell surface antibodies.

- However, Ab is not present in all PNS → ultimately a clinical diagnosis.
# Neurologic Paraneoplastic Syndrome

## Peripheral NS involvement
- More common than CNS involvement
- Ex. MG, LEMS, AIDP
- Could be responsive to immunomodulatory Rx: LEMS, MG, AIDP

## CNS involvement
- Example: cerebellar degeneration, limbic encephalitis, opsoclonus-myoclonus
- Subacute progression over weeks to months
- Can render a previously fit patient bedbound
- Usually resistant to immunomodulatory Rx (exception: antiNMDA, limbic encephalitis)
- Prognosis is poor
- CSF: Early → inflammatory (pleocytosis, high protein) → decline with time
- Brain imaging: usually unremarkable except limbic encephalitis & cerebellar degeneration
Estimated Likelihood That a Given Neurologic Disorder Is a Paraneoplastic Syndrome

<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, GI</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>
Limbic Encephalitis

- **Clinical:**
  - Short-term memory deficit (80%) with intact cognitive Fn.
  - +/- partial complex seizure (50%),
  - confusion (40%), psychiatric symptoms (40%)

- Related syndrome: brainstem encephalitis, encephalomyelitis

- Frequently preceded Dx of cancer but 40% may occur AFTER cancer diagnosis

- One of a few CNS paraneoplastic syndrome that brain image helps: abnormal signal in hippocampus

- **DDx:** herpes encephalitis, other autoimmune limbic encephalitis, Wernicke encephalopathy, psychiatric disorder

- **CA:** Small cell lung cancer*, testicular CA^, breast CA, thymoma”, ovarian teratoma

- **Ab:** Anti-Hu*, Anti-Ma1-2^, Anti CV2”, Anti AMPA, Anti NMDA, anti LGI1

- Occasionally improved with Rx of primary CA
ชาย 51 ปี ผู้สูงอายุ ป่วยเป็นการวิบัติศีรษะ

- **CC**: ทำ process การทำงานไม่ได้ 1 wk PTA

- 1 wk PTA ตื่นเช้าไปทำงานตามปกติ แต่เริ่มทำงานแล้วจ่ากระบวนการทำงานไม่ได้ จ่าขั้นตอนการเจาะเงินให้พนักงานไม่ได้ ต้องหยิบเอกสารเก่าขึ้นมาดูแล้วพนักงานก็ออก ต่อมาทำไปจนจบได้ แต่ตื่นกลางวันโดยตรง ทำ BTS ได้ ทำกิจวัตรประจำวันอื่นได้ตามปกติ

- ปกติเคยไปบ้านน้องสาวหลายครั้งแต่ตอนนี้นึกไม่ออก

- ไม่มีไข้ ไม่มีปวดศีรษะ ไม่มีผื่นตามตัว ไม่มีอ่อนแรง/เจ็บ ไม่มีเหงือกแย่ที่เห็นภาพหลอน

- **PH**: สูบบุหรี่ 20 ผืน/วัน x 20+ yrs , alcohol 1-2 bottles/wk, no drugs abuse

PE: unremarkable

Neuro: alert, orientation ✓

MMSE: 29/30

Impaired executive function
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, B1/B12 def, prion dz (CJD), MS/demyelination, ADEM
- **Most common ass. 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
Lambert-Eaton Myasthenia Syndrome

- Paraneoplastic in 50-60% \(\rightarrow\) Small cell CA (but only 5% of SCLC have LEMS)
- **clinical point**: decreased DTR which improves after repetitive movement
- can be ass. 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 stm.
- Antibody against P/Q type voltage gated Ca channel (VGCC) (pre-synaptic) \(\rightarrow\) prevent entry of calcium into the cell (necessary for release of Ach)
- VGCC: Can be detected in both paraneoplastic and autoimmune 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
  - May be rarely ass. With other CA: SCLC, breast, lymphoma
  - CN involvement more common than in LEMS (ptosis, bulbar)
- EMG: decremental compound muscle action potential w/ repetitive stimulation \(\rightarrow\) then stabilizes or increasing afterwards
- Anti-AchR +/- other muscle protein Ab \(\rightarrow\) 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
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, several myositis-specific autoAb (anti-Jo, antisynthetase, antiSRP, etc)
- Anti TIF1 gamma (anti p155), Anti NPX2: significant association with cancer-ass. myositis
  - NPV 95%, PPV 53% (Arthritis Rheum 2012) ➞ may aid in extent of work-up
(Paraneoplastic) 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, ENT exam for NPC
  - Routine labs: CBC, chem., UA, CXR, FOBT
  - **Age-appropriate cancer screening**: MMG, PV, colonoscopy
  - If symptomatic (wt loss, anorexia, localizing symptoms, older age) → CT chest / abdomen has higher yield than tumor markers, ? Role of PET/CT?
  - Tumor markers: no real use..? CA125, PSA, CA19-9
    - Higher OR of cancer with elevated baseline value
  - Continued periodic screening for up to 4-5 years

- **High risk group**: older age>45, cutaneous vasculitis/necrosis, dysphagia, absence of ILD, absence of muscle-specific Ab, anti TIF1/ NPX2 +ve

- **Treatment**: Some improve w/ Rx of CA, but usually **immuno Rx needed**
  - Prednisone, azathioprine, MTX → most do not recover completely

*Lu X. Plos One*
Paraneo plastic Syndrome

- Neurological
- Endocrine
- Renal
- Dermatological
- Hemato.
- others
Metabolic & Endocrinologic Paraneoplastic Syndrome

- Usually correlated to tumor activity/size
- Ectopic production from non-endocrine tumor
  - Ectopic ACTH from bronchial carcinoid tumor
  - PTHrP from CA cervix
- Eutropic hormone production from endocrine tumor
  - Insulinoma, glucagonoma: pancreatic islet cell
  - Calcitonin production from medullary thyroid C-cell

Treatment

- Tumor removal, systemic control
- Medical treatment to reduce consequence of hormone production: ketoconazole, bisphosphonate, etc
### Paraneoplastic Syndromes Caused by Ectopic Hormone Production

<table>
<thead>
<tr>
<th>Paraneoplastic Syndrome</th>
<th>Ectopic Hormone</th>
<th>Typical Tumor Type</th>
</tr>
</thead>
</table>
| Hypercalcemia of malignancy | Parathyroid hormone-related protein (PTHrP) | • Squamous cell (head and neck, lung, skin, esophagus, cervix),  
• NSCLC: large cell, adenoCA  
• breast, bladder, kidney, HCC, cholangioCA |
| Syndrome of inappropriate antidiuretic hormone secretion (SIADH) | 1,25 dihydroxy vitamin D | Lymphomas |
| Cushing's syndrome | Vasopressin | • Lung (small cell, squamous),  
• gastrointestinal, genitourinary, head&neck |
| Cushing's syndrome | Adrenocorticotropic hormone (ACTH) | • Lung (small cell, bronchial carcinoid)  
• Neuroendocrine tumor : thymus, pancreatic islet, medullary thyroid carcinoma |
| Corticotropin-releasing hormone (CRH) (rare) | Pancreatic islet, carcinoid, lung, prostate |
Paraneoplastic Syndromes Caused by Ectopic Hormone Production

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<th>Paraneoplastic Syndrome</th>
<th>Ectopic Hormone</th>
<th>Typical Tumor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-islet cell hypoglycemia</td>
<td>insulin-like growth factor (IGF) II</td>
<td>• Mesenchymal tumor: fibrosarcoma &amp; others, mesothelioma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HCC, gastric, prostate CA</td>
</tr>
<tr>
<td>Oncogenic osteomalacia</td>
<td>Fibroblast growth factor 23 (FGF23)</td>
<td>Mesenchymal tumor: usu. benign</td>
</tr>
<tr>
<td>Male feminization</td>
<td>B hCG share a homologous alpha subunit with TSH</td>
<td>Testicular cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HCC, NSCLC</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>hCG → TSH-like</td>
<td>Testicular cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydatidiform mole</td>
</tr>
<tr>
<td></td>
<td>TSH</td>
<td>Struma ovarii (rare)</td>
</tr>
</tbody>
</table>
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)

- High plasma ACTH levels (>100 pg/ml) and do not respond to high dose dexa suppression (in contrast to ACTH-producing pituitary tumor)
Ectopic ACTH Syndrome

- Most are associated with
  - lung cancer (50%): small cell (most common) > NSCLC
  - Pancreatic neuroendocrine tumor
  - Thymic carcinoid / bronchial carcinoid
- Work-up: CXR, CT chest → CT upper abdomen
- Prognosis depends on tumor type and disease stage
  - Small cell lung CA: highly aggressive, most die within 1-2 years,
  - Carcinoid tumor/ Pancreatic NET: can be indolent
- Patients with paraneoplastic Cushing → shorter survival than those without Cushing (Higher incidence of infection)
- Supportive Rx: adrenalectomy, ketoconazole, Etomidate IV (IPD only), mitotane, Aminogluthethimide/ metyrapone (not available in Thailand)
ชาย 61 ปี DLP, non alcoholic

2 wks PTA: หลังตื่นนอน มีอาการเวียนศีรษะ เป็นบางครั้ง ไม่มีบ้านหมุน ไม่มีคลื่นไส้อาเจียน ไม่ปวดศีรษะ ไม่มีชา

เคยไปรักษาที่คลินิกใกล้บ้าน ได้ยาแก้เวียนศีรษะมากิน อาการดีขึ้นเล็กน้อย ไม่มีช่วงอาการหายดัน

Last well seen 15 hr PTA เวลาประมาณ 18:00 น. ผู้ป่วยรับประทานอาหารเย็น จากนั้นเข้านอนตามปกติ

30 min PTA ยาดื้อไปพบ เรียกไม่รู้สึกตัว ไม่มีอุจจาระ/ปัสสาวะราด ไม่มีลิ่มทวาร/กระตุกแขนขา ญาติจึงนำส่งโรงพยาบาล

V/S: BP OK, SpO2 96% Room air, drowsy
POCT-glu : 28 mg%
Abd: liver span 9 cm, no splenic dullness, palpable mass about 10 week size, smooth surface at lower part of abdominal, firm consistency, fixed

• Insulin <1.6, C-peptide 0.023
• Dx : Non-Islet Cell Hypoglycemia
• Production of (pro)IGF II → GH suppression
• Supportive Rx : Glucose, nocturnal meal
  • Glucocorticoid / glucagon/ growth hormone

Solitary fibrous tumor
Paraneo plastic Syndrome

- Neurological
- Endocrine
- Renal
- Dermatological
- Hemato.
- others
Fever

- Hypothalamus is a thermostat of the body
- Resetting the thermostat allows for higher body temperature
- Pyrogenic cytokines produced by the tumor (IL-1, TNF, IL-6, IL-12, IFN)
- Although any tumors can cause fever, the most common are
  - Lymphoma, leukemia
  - HCC, RCC,
  - Pediatric sarcoma: ewing's, rhabdomyosarcoma, osteosarcoma
  - Extensive liver metastasis
  - Bulky tumor with necrosis
- Needs to R/O infection
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
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 success in cancer Rx
Paraneo plastic Syndrome

- Neurological
- Endocrine
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- Hemato.
- others
New Treatment-Related Complications
Molecular targeted therapy: it is making a difference

Median survival (months)

1980s
1990s
2000s
2013
2018

BSC: 2–5 months
Single-agent platinum: 6–8 months
Platinum-doublets: 8–10 months
Targeted therapies: >18 months
immunoRx > 24 m

Immune Checkpoint Inhibitors FDA Approved in Multiple Cancers as of April 2020

- ICIs now approved as monotherapy and in combination with other ICIs or CT
- Patients may receive ICI therapy for yrs, as optimal duration is unknown
  - Initial strategy was continuing ICI until progression/toxicity or to 2 yrs
- ICIs also introduce the potential for new toxicity \(\rightarrow\) Immune-related AEs
- Activation of immune cells in nontumor compartments
- Can mimic autoimmune conditions


Slide credit: clinicaloptions.com
A New Spectrum of Adverse Events

Skin
- Dermatitis, erythoderma
- Erythema multiforme
- Stevens–Johnson syndrome
- Toxic epidermal necrolysis
- Psoriasis
- Vitiligo
- Alopecia

Eyes
- Conjunctivitis
- Uveitis, iritis, retinitis
- Scleritis, episcleritis
- Blepharitis

Endocrine system
- Hypo- or hyperthyroidism
- Hypophysitis, hypopituitarism
- Adrenal insufficiency
- Type 1 diabetes

Cardiovascular system
- Myocarditis
- Pericarditis
- Vasculitis

Liver
- Hepatitis

Kidneys
- Nephritis
- Lupus-like glomerulonephritis

Neurologic system
- Neuropathy
- Myelopathy
- Guillain–Barré syndrome
- Myasthenia gravis–like syndrome
- Encephalitis, meningitis

Gastrointestinal tract
- Colitis
- Ileitis
- Pancreatitis
- Gastritis
- Perforation

Musculoskeletal system
- Arthralgias, arthritis
- Myalgias, myositis

Lungs
- Pneumonitis
- Pleuritis
- Interstitial lung disease

Organs affected by and manifestations of immune-related adverse events.

Slide credit: clinicaloptions.com
Most Immune-Related Adverse Events (Except Endocrine) Resolved within 6 Weeks with Steroids / Immunosuppression

- usually start within the first few weeks to months after treatment but can occur anytime, even after treatment discontinuation
- Dermatologic adverse events are usually the first to appear.


Slide credit: clinicaloptions.com
## Typical Presentations of Common irAEs

<table>
<thead>
<tr>
<th>Common irAE</th>
<th>Typical Presentation</th>
</tr>
</thead>
</table>
| Dermatologic\(^{[1,2]}\)  | • Maculopapular rash with or without pruritus, predominantly on trunk and to lesser extent the upper limbs, spreading to extremities;  
• Eczematous, lichenoid, psoriasiform manifestations;  
• Blistering skin reactions                                                                 |
| Diarrhea/colitis\(^{[2]}\) | • Diarrhea, abdominal pain, hematochezia, weight loss, fever, vomiting  |
| Hepatic\(^{[2]}\)       | Often asymptomatic and diagnosed via routine blood tests                                                                                               |
| Pancreatic\(^{[1]}\)    | Asymptomatic elevation in amylase/lipase; CT, clinical findings of pancreatitis; severe abdominal pain, vomiting, and hemodynamically unstable       |
| Endocrine\(^{[2,3]}\)   | • Hypophysitis: headache, visual disturbances, fatigue, altered consciousness, deranged electrolytes (particularly hyponatremia), mood changes  
• Hypo/hyperthyroidism                                             |

Slide credit: [clinicaloptions.com](http://clinicaloptions.com)
Dermatologic Reactions in Patients Treated With Immune Checkpoint Inhibitors

Grade 3 Maculopapular Rash

Oral mucositis with ulceration

After steroid rinse
Dermatologic Reactions in Patients Treated With Immune Checkpoint Inhibitors

Bullous Pemphigoid Combining Maculopapular Rash and Blisters (Green Circles)

Vasculitis With Digit Necrosis and Apparent Livedo


Slide credit: clinicaloptions.com
Small cell lung cancer
ChemoRx + durvalumab

Drug induced LE

ANA 1:320
Anti SS-A +ve

Rx: Prednisolone
51 yo male with metastatic melanoma Rx’ed with Nivolumab x 3 months with partial response

presents to the emergency department after falling in the bathroom → Fx fibula

1 mo ago, he was feeling increasingly tired but was still able to work
9 days ago, he experienced fatigue, dizziness, and dehydration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na, mEq/L</td>
<td>130</td>
<td>135-145</td>
</tr>
<tr>
<td>TSH, µU/mL</td>
<td>2.9</td>
<td>0.5-5.0</td>
</tr>
<tr>
<td>Free T4, ng/dL</td>
<td>0.8</td>
<td>0.9-2.3</td>
</tr>
<tr>
<td>AM cortisol, mcg/dL</td>
<td>0.6</td>
<td>5-25</td>
</tr>
<tr>
<td>AM ACTH, pg/mL</td>
<td>60</td>
<td>9-52</td>
</tr>
</tbody>
</table>

- Dx: adrenal insufficiency from immune checkpoint inhibitors
- Rx: hydrocortisone at 50 mg IV, followed by oral doses of 15 mg AM and 10 mg early afternoon
- Nivolumab held and resumed after fully supplemented
- Instructed on stress doses of hydrocortisone, recommended to wear medic alert bracelet
Immune-Related Hypophysitis

- Rare <6%, mean onset 6 weeks
- **Symptom:**
  - non-specific: headache, N/V
  - hormone-specific symptom: DI, hypothyroid, adrenal
  - Severe symptom: headache and visual change due to gland edema or profound dizziness and nausea from an adrenal crisis
- **Differential diagnoses:**
  1. Disease progression
  2. Brain metastases
  3. Pituitary metastases
  4. Pituitary bleeding
  5. Meningitis
- **Lab:** early indicator: low TSH
  - If suspected: morning cortisol, ACTH, TSH, LH and FSH, E2, testosterone, prolactin
  - Monitor cortisol, ACTH, TSH
Immune-Related Hypophysitis

• **MRI finding:** pituitary enlargement, nodularity
  25% had normal pituitary gland → atrophy
  (inflammation → fibrosis)

• Prompt therapy will ameliorate symptoms and permits continued Rx
  • Physiologic dose prednisolone may be adequate
  • Higher dose in symptomatic cases: headache, visual changes
  • May need other hormonal replacement: thyroxine, sex H.

• May be irreversible
Immunotherapy-related Pneumonitis

• Fairly uncommon, but potentially serious

• Pts at increased risk for pneumonitis
  • NSCLC in the setting of chronic lung inflammation
  • Prior radiation to lung
  • History of COPD

• Signs and symptoms
  • Shortness of breath
  • Dry cough
  • Low O2 saturation
  • Increasing oxygen requirements
  • Asymptomatic (may be detected just on imaging)

• Must DDx with
  • Disease progression
  • infection

• In severe cases, Rx with 2 mg/kg of IV methylprednisone and consideration of additional immunosuppression including infliximab, mycophenolate, cyclophosphamide if necessary
NSCLC, 3rd line anti-PD1 Rx

Baseline

After 1 cycle of Nivolumab
Less dyspnea

After 2 cycles
worsening symptoms
1 week after treating with high dose steroid
Less Common IrAEs

- Hematologic (hemolytic anemia, thrombocytopenia)
- Cardiovascular (myocarditis, pericarditis, vasculitis)
- Ocular (blepharitis, conjunctivitis, iritis, scleritis, uveitis)
- Renal (nephritis)
- Musculoskeletal: Joint pain, swelling; inflammatory symptoms; stiffness after inactivity, myositis
- Several case reports of rare autoimmune-based toxicities in pts treated with ipilimumab
  - Lupus nephritis
  - Inflammatory enteric neuropathy
  - Tolsosa-Hunt syndrome
  - GBS
  - Myocardial fibrosis
  - Acquired hemophilia A
  - Autoimmune polymyositis
Cardiovascular Events

- High mortality with cardiac irAEs: 23%[^3]
  - Demise secondary to conduction abnormality most common; preserved ejection fraction[^2]
- Cardiac irAEs co-occur with noncardiac irAEs in > 50% of cases[^2]

**Cardiotoxicity Presentation[^1,2]**
- Pericarditis
- Arrhythmias
- Cardiomyopathy
- Cardiac fibrosis
- Heart failure
- Cardiac arrest

**Myocarditis**—most common
  - Prevalence with anti–CTLA-4 + anti–PD-1: 1.14%[^1,4]
  - Median onset: 34 days[^3]
  - Symptoms: myalgia, SOB, chest pain[^2]
  - Associated with myositis and myasthenia gravis[^5]

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Take-home Messages

- Life threatening hyperimmunity is possible
- Side effects are usually delayed by months after 1\textsuperscript{st} dose
- Can occur after discontinuing ICI
- Challenging and evolving events to internists
  - Disease progression vs irAE vs infection
  - Call treating oncologists & consult other specialists
  - Delayed diagnosis and treatment may lead to poor outcome

- Steroid can reverse nearly all toxicities, but should be reserved for grade 3-4
THANK YOU FOR YOUR ATTENTION