Oncologic Emergencies and Paraneoplastic Syndromes

Internal Medicine Board Review

Amy M. Weise D.O.

Assistant Professor of Medicine

Oncologic Emergencies

- Why should I learn this?
  - Cancer therapy is largely outpatient, so these patients are likely to walk into your office.
  - Treatment should not be delayed while attempting to contact the oncologist.
  - May be the presenting symptom
  - Board Exams

Oncologic Emergencies

- Definition: Acute condition caused by cancer or the treatment of cancer where early recognition and intervention would result in the avoidance of mortality or permanent morbidity.

Oncologic Emergencies

- Initial Evaluation:
  - Brief focused history
  - Focused Exam
  - Lab/radiograph review
  - Initial Intervention and Additional Studies
  - Then comprehensive history and exam

Oncologic Emergencies

- Categories:
  - Metabolic
  - Hematologic
  - Structural
  - Treatment related

Metabolic: Tumor Lysis Syndrome

- Definition: acute lysis of tumor cells as a result of chemotherapy or radiation therapy, usually within 72 hours of therapy
- Tumor Types:
  - Leukemia
  - High-grade lymphoma
  - SCLC

Metabolic: Tumor Lysis Syndrome

- Features:
  - azotemia
  - acidosis
  - hyperphosphatemia
  - hyperkalemia
  - hypocalcemia
  - hyperuricemia
  - ARF
- Symptoms:
  - Nausea
  - Vomiting
  - Weakness
  - Fatigue
  - Neuromuscular irritability
  - Arrhythmia

Metabolic: Tumor Lysis Syndrome

- Tx/Prevention:
  - fluids
  - allopurinol
  - rasburicase
  - urine alkalinization
  - HD
  - kayexalate
  - phos-lo

Metabolic: Hypercalcemia

- Seen in 20 to 30% of cancer patients
- Rate of calcium mobilization from bone exceeds renal calcium excretion
- Tumor Types:
  - Multiple myeloma
  - Squamous Cell: lung, H&N, esophagus
  - Breast
  - Kidney

Metabolic: Hypercalcemia

- Mechanisms:
  - Bone Mets- osteoclast activity
  - Parathyroid hormone-related peptide (binds PTH receptors)
  - Calcitriol production- lymphoma
  - Co-existing Primary Hyperparathyroidism
  - Osteoclast activating factor (OAF)- Multiple Myeloma

Metabolic: Hypercalcemia

- Treatment:
  - Calcitonin — increases renal calcium excretion and by decreasing bone reabsorption
  - Bisphosphonates — inhibit calcium release from bone by interfering with the metabolic activity of osteoclasts, and is cytotoxic to osteoclasts. (Pamidronate, zoledronic acid, ibandronate and etidronate)

Metabolic: Hypercalcemia

- Treatment
  - Glucocorticoids (eg, prednisone in a dose of 20 to 40 mg/day) will usually reduce serum calcium concentrations within two to five days by decreasing calcitriol production and OAF
  - Volume expansion with isotonic saline
  - Loop diuretic will also contribute to increased calcium excretion by inhibiting calcium reabsorption in the loop of Henle
  - Hemodialysis

Metabolic: SIADH

- Definition: An inappropriate elevation in ADH release that produces hyponatremia by interfering with urinary dilution/excretion of water.
- Tumor Types:
  - small cell carcinoma of the lung
  - other lung tumors
  - duodenum
  - pancreas
  - olfactory neuroblastoma

Metabolic: SIADH

- Symptoms:
  - Anorexia
  - Nausea
  - Myalgia
  - Headaches
  - Seizures
  - Coma
- Lab:
  - Low sodium
  - Low serum osmolarity
  - Concentrated urine

Metabolic: SIADH

- Treatment:
  - Water restriction is the mainstay of therapy in asymptomatic hyponatremia
  - Hypertonic saline (or salt tablets)
  - Loop Diuretic- lowers the urine osmolality and increases water excretion by impairing the renal responsiveness to ADH
  - Demeclocycline and lithium act on the collecting tubule cell to diminish its responsiveness to ADH

Metabolic: SIADH

- Remember to exclude other causes of hyponatremia
  - Medications: vincristine, cyclophosphamide
  - Adrenal insufficiency
  - Brain mets

Hematologic: Febrile Neutropenia

- Neutropenia and Risk:
  - Risk of an occult infection increases with an ANC <1,000 cells/microL
  - It is substantially higher for those with an ANC <500 cells/microL
  - And is highest for those with an ANC <100 cells/microL
  - A rapid decline in ANC
  - Prolonged duration of neutropenia (>7 to 10 days)

Hematologic: Febrile Neutropenia

- Defined as a single temperature of >38.3ºC (101.3ºF), or a sustained temperature >38ºC (100.4ºF) for more than one hour
- Patients may present with hypothermia, hypotension, or clinical deterioration as the initial signs of occult infection.
- Consequently there should be a low threshold for starting empiric antibiotics

Hematologic: Febrile Neutropenia

- Most common pathogens:
  - S. *aureus*
  - S. *epi*
  - Streptococcal species
  - Others: Candida albicans, aspergillus, Fusarium, viral
  - Most often the source goes unidentified

Hematologic: Febrile Neutropenia

- Work Up:
  - Blood Cultures: peripheral and line
  - Urine Cultures
  - CXR-may not see infiltrate
  - CT chest if fever persist after 4-7 days
  - LP if clinically indicated

Hematologic: Febrile Neutropenia

- Monotherapy
  - Beta-lactam carbapenem- meropenem, imipenem, piperacillin tazobactam
  - 4th generation cephalosporin-ceftazidime, cefepime
- Dual Therapy
  - Aminoglycoside Plus Beta-lactam
  - Fluoroquinolone Plus Beta-lactam

Hematologic: Febrile Neutropenia

- Vancomycin- if line associated, cellulitis, severe mucositis, hypotension, history of MRSA colonization, or recent quinolone prophylaxis, patients with clinical deterioration or persistent fever despite empiric antibiotics.
- Anti-fungal- fever persists after 4-7 days

Hematologic: Febrile Neutropenia

- 70% mortality rate if initiation of antibiotics is *delayed*

Hematologic: Hyperviscosity Syndrome

- Results from high levels of serum proteins
- Classically, the syndrome is a result of increased amounts of IgM, as seen in Waldenstrom's macroglobulinemia
- Multiple myeloma in which abnormal polymers of IgA, IgG, or kappa light chains are produced

Hematologic: Hyperviscosity Syndrome

- Impairment in the microcirculation of the CNS
- Headache
- Dizziness
- Vertigo
- Nystagmus
- Hearing loss
- Visual impairment
- Somnolence
- Coma
- Seizures
- Mucosal hemorrhage
- Heart failure
- Renal failure
- Sausage-like beading in the retinal veins

Hematologic: Hyperviscosity Syndrome

Hematologic: Hyperviscosity Syndrome

- Severe neurologic impairment, such as stupor or coma, should be treated with plasma exchange on an emergency basis
- Chemotherapy for the underlying cause
- AVOID pRBC TRANSFUSIONS

Structural: SVC Syndrome

- Definition: Partial or complete obstruction of blood flow through the SVC to the Right atrium
- Causes:
  - compression
  - invasion
  - thrombosis
  - fibrosis

Structural: SVC Syndrome

- Tumor Types:
  - Lung
  - NHL
  - Thymoma
  - Germ cell
  - Breast

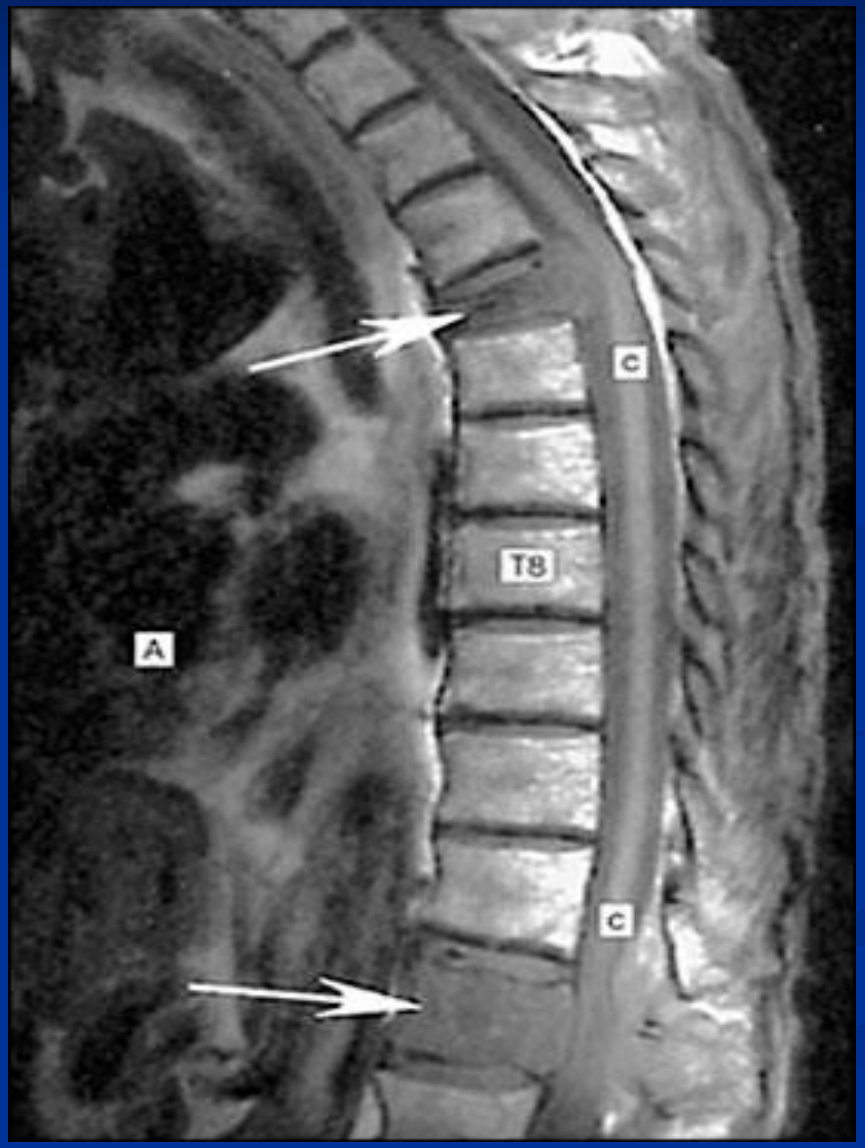
Structural: SVC Syndrome

- Signs:
  - JVD
  - Venous dilation of chest wall
  - Facial edema
  - Upper extremity edema
  - Papilledema if onset is rapid
- Symptoms
  - Head fullness or pressure
  - Cough
  - Dyspnea
  - Chest pain
  - dysphagia

Structural: SVC Syndrome

- Treatment:
  - SVC stent
  - XRT
  - Chemotherapy
  - Anti-coagulants or thrombolytics
- Pearls:
  - Secure an accurate diagnosis with biopsy
  - Oxygen
  - Elevate HOB
  - Diuretics sparingly if at all

Structural: Cord Compression



Structural: Cord Compression

- Occurs in 1-5% of cancer patients
- 95% are caused by extradural metastases involving the vertebral column
  - T-Spine: 70% (spinal canal is narrowest here)
  - L-Spine: 20%
  - C-Spine: 10%

Structural: Cord Compression

- Tumor Types:
  - Lung
  - Breast
  - Unknown primary
  - Prostate
  - Renal

Structural: Cord Compression

- Symptoms:
  - Pain, Pain, Pain- localized or radicular, worse with movement, cough, sneeze
  - Urinary retention/incontinence (late)
  - Constipation (late)
  - Poor prognostic features: paralysis or urinary retention

Structural: Cord Compression

- Dx: MRI
- Treatment:
  - Narcotics
  - Dexamethasone: dose is controversial
    - Initial: 20-100mg IV bolus
    - Maintenance: 6-16mg q 6 hours
  - XRT
  - Neurosurgery- spine stabilization

Structural: Cord Compression

- Permanent neurologic impairment can result if treatment is delayed by only a few hours
- Major quality of life issue that might be preventable

Paraneoplastic Syndromes

- Paraneoplastic neurologic syndromes are a heterogeneous group of neurologic disorders caused by mechanisms other than metastases, metabolic and nutritional deficits, infections, coagulopathy or side effects of cancer treatment.
- These syndromes may affect any part of the nervous system from cerebral cortex to neuromuscular junction and muscle.

Paraneoplastic Syndromes

- The more common syndromes
  - Lambert-Eaton myasthenic syndrome affects 3% of patients with small-cell lung cancer
  - Myasthenia Gravis affects 15% of all patients with thymoma
  - <1% incidence for other solid tumors

Paraneoplastic Syndromes

- Review Article: "Paraneoplastic neurological syndromes" in Orphanet Journal of Rare Diseases May 2007, 2:22
- Occur in < 0.01% of cancer patients

Paraneoplastic Syndromes

- Pathogenesis:
  - Onconeural antibodies: antibodies directed at tumor antigens that cross-react with components of the nervous system
  - 50% of patients with PNS do not have detectable antibodies
  - Antibodies may be present in the absence of a PNS

Paraneoplastic Syndromes

- Definite PNS Criteria:
  - Classical neuro syndrome and cancer develops within 5 years of the neuro disorder
  - Non-classical neuro syndrome improves after treatment of underlying cancer
  - Non-classical neuro syndrome with onconeural antibodies AND cancer develops within 5 years
  - Neuro syndrome with well-characterized onconeural antibodies (Hu, Yo, CV2, Ri, Ma2, anphiphysin) AND no cancer

Paraneoplastic Syndromes

- Possible Criteria:
  - Classic neuro syndrome, No Ab, No cancer, but is at high risk for an underlying tumor
  - Neuro syndrome, partially characterized Ab, No cancer
  - Non-classical neuro syndrome, No Ab, cancer diagnosis within 2 years

Paraneoplastic Syndromes

- Anti-Hu (antineuronal nuclear antibody ANNA-1)
  - Encephalomyelitis- asymmetric paresthesias SCLC
  - Limbic encephalitis- memory and mood
- Anti-Yo: Cerebellar degeneration- dysarthria and ataxia
- Anti-Tr: Cerebellar degeneration (Hodgkin's)

Paraneoplastic Syndromes

- Anti-Ta: Limbic encephalitis (testicular/breast)
- Anti-amphiphysin: Stiff-person syndrome
- Anti-GAD: Stiff-person syndrome (breast)
- LEMS Ab: Lambert-Eaton, SCLC

PNS: Lambert-Eaton myasthenic syndrome

- Disorder of reduced acetylcholine (ACh) release from the presynaptic nerve terminals

- Antibodies directed against the voltage-gated calcium channel (VGCC) interfere with the normal calcium flux required for the release of acetylcholine

PNS: Lambert-Eaton myasthenic syndrome

- Symptoms
  - slowly progressive proximal muscle weakness, particularly involving the legs
  - Deep tendon reflexes are typically depressed or absent
  - Ptosis and diplopia
  - Dry mouth
  - Erectile Dysfunction
  - Respiratory failure may occur late in the course.

Hallmark: Recovery of lost deep tendon reflexes or improvement in muscle strength with vigorous, brief muscle activation

PNS: Lambert-Eaton myasthenic syndrome

- Diagnosis:
  - Post-exercise facilitation: Maximal isometric contraction the limb for 10 to 15 seconds may lead to temporary reappearance of previously depressed or absent DTR's, and temporary improvement of muscle weakness.
  - Ab to voltage-gated calcium channel (VGCC)
  - Electrodiagnostic studies-EMG

PNS: Lambert-Eaton myasthenic syndrome

- Occurs much less frequently than myasthenia gravis
- Approximately one-half of LEMS cases are associated with a malignancy, usually SCLC

PNS: Myasthenia gravis

- Mediated by autoantibodies against the acetylcholine receptor (AChR-Ab)
- The majority of patients AChR-Ab positive myasthenia gravis have thymic abnormalities: hyperplasia in 60 to 70% and thymoma in 10 to 12%

PNS: Myasthenia gravis

- Symptoms
  - fluctuating skeletal muscle weakness, worse later in the day or evening
  - fatigue- meaning worsening contractile force of the muscle
  - 50% of patients present with ocular symptoms of ptosis and/or diplopia
  - 15% present with bulbar symptoms (dysarthria, dysphagia, and fatigable chewing)
  - Less than 5% present with proximal limb weakness alone
  - Respiratory insufficiency

PNS: Myasthenia gravis

- Diagnosis
  - Tensilon test- Edrophonium chloride is an acetylcholinesterase inhibitor prolongs the presence of Ach in the neuromuscular junction and results in an immediate increase in muscle strength
  - Serologic tests for autoantibodies
  - Electrophysiological studies

PNS: Myasthenia gravis

- Treatments:
  - Symptomatic treatments (anticholinesterase agents)
  - Chronic immunomodulating treatments (corticosteroids and other immunosuppressive drugs)
  - Rapid immunomodulating treatments (plasma exchange and intravenous immune globulin)
  - Surgical treatment (thymectomy)

Others

- Carcinoid Syndrome
  - Carcinoid tumors of foregut derivatives (small intestine, stomach, bronchus, pancreas, thyroid)
  - Overproduce 5-HT (5-hydroxytryptamine) serotonin, histamine, tachykinins, kallikrein and prostaglandins
  - Urine excretion of 5-HIAA

Carcinoid Syndrome

- Symptoms:
  - Episodic flushing
  - Fall in blood pressure and rise in pulse rate
  - Secretory diarrhea
  - Wheezing and dyspnea
  - Carcinoid heart disease- right side

Carcinoid Syndrome

- Treatment:
  - Somatostatin analog octreotide
  - Cyproheptadine, a serotonin antagonist
  - Chemotherapy effectiveness is questionable
  - Isolated lesions: cryo, RFA (treat with octreotide prior to anesthesia to prevent crisis)

Others

- Zollinger-Ellison Syndrome- excessive gastrin secretion from a gastrinoma
- Develop peptic ulcers, most are in the first portion of the duodenum
- Diarrhea can also be a prominent feature

ZES

- Diagnosis:
  - Fasting serum gastrin concentration
  - Secretin stimulation test
  - Gastric acid secretion studies

- 50 yo female, presents to ER c/o falling, difficulty arising from a chair. Weakness improved during the day. Also c/o dyspnea on exertion. 45 pack years.
- Proximal muscle weakness on exam

- What is the most appropriate management?

- A. Follow up with PCP
- B. Physical Therapy
- C. Admit for EMG and possible treatment
- D. Smoking cessation classes

Questions obtained from The John Hopkins Internal Medicine Board Review 2004

- 56yo female presents to ER c/o epistaxis, blurry vision, confusion.
  PMHx: HTN
- Vs all normal, blood at nares and gums, bibasilar crackles, no edema
- Labs: Hgb-8, plts-350, WBC-8.0, normal diff., T. ptn 10.2, albumin 3.0, lytes all normal

- What is the most likely diagnosis?
  - A. Essential thrombocythemia
  - B. CML
  - C. AML
  - D. Hyperviscosity

Questions obtained from The John Hopkins Internal Medicine Board Review 2004

- What is the most appropriate therapy?

- A. Platelet transfusion
- B. pRBC transfusion
- C. Plasmapheresis
- D. Prednisone

- What tests or physical exam findings will assist in finding the diagnosis in the ER?

- A. CT brain
- B. Serum viscosity
- C. Fundoscopic exam
- D. B and C

Questions obtained from The John Hopkins Internal Medicine Board Review 2004

- 65yo man presents to the ER with confusion, increased thirst, and increased urination. PMHx: HTN
- Vs normal , dry mm, skin tenting
- Labs: Cr=5.4, BUN=46, K=5, Ca=12.5, Alb=3.0, T. protein=9

- What is the most appropriate initial therapy?

- A. Normal saline
- B. Dialysis
- C. Pamidronate
- D. Diuretics

Questions obtained from The John Hopkins Internal Medicine Board Review 2004

Thank You and Best of Luck!