Oncologic Emergencies

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What constitutes an oncologic emergency?

- Complications arising from
  - Cancer
  - Paraneoplastic syndrome
  - Treatment of cancer

- Requires immediate attention and reversal
Outline

- Hyperleukocytosis
- Tumor lysis syndrome
- Disseminated intravascular coagulation
- Hypercalcemia
- Thrombotic thrombocytopenic purpura/HUS
- Hyperviscosity
- Spinal cord compression
- SVC Syndrome
Hyperleukocytosis

- 5-20% of adults dx’d with AML

- 3 main complications of HL include:
  - Leukostasis
  - DIC
  - Tumor lysis syndrome

- Early mortality increased in AML patients with HL

- Shorter overall survival
Pathogenetic mechanisms in leukostasis

Christoph Röllig, and Gerhard Ehninger Blood 2015;125:3246-3252
Clinical

- Unexplained fever
- Fatigue
- Weight loss
- Bone pain
- Bruising/Bleeding
- Gum hypertrophy
- Hepatosplenomegaly
- AMS
- Hypoxia

Lab

- Abnormal CBC – Leukocytosis or pancytopenia
- Coagulopathy/DIC
- High LDH
- Peripheral smear
Management of HL

*Definitive treatment*

Hydroxyurea 1-3 g PO q 6 hours

Leukopheresis
Leukoreduction Apheresis

- Rapidly removes excess leukocytes by mechanical separation
- Single round of leukopheresis reduced WBC by 10-70%
- Debate:
  - Majority of leukemic burden in marrow
  - Beneficial clinical effect on early outcomes could not be shown consistently in clinical trials
Leukoreduction Apheresis

- Contraindications
  - Hemodynamic instability
  - Coagulopathy
  - Cardiovascular comorbidities

- No evidence for clinical benefit in HL patients without leukostasis symptoms

- Given pros and cons, routine leukopheresis can not be routinely recommended.
Tumor Lysis Syndrome

- TLS is the most common oncologic emergency.
- Constellation of metabolic abnormalities resulting from either spontaneous or chemotherapy-induced tumor cell death
Tumor cell lysis

Release of DNA

Purines

Hyperphosphatemia

Hypoxanthine/Xanthine

Xanthine oxidase

Uric acid

Rasburicase

Uricase

Allantoin

Allopurinol

Ca-phos precipitation

Hyperkalemia

Cardiac arrhythmias

Hypocalcemia

Urate nephropathy

Ca-phos nephropathy
Risk factors for TLS

- Clinical
  - Large tumor burden with rapid cell turnover (acute leukemias, lymphomas)
  - Sensitivity of tumors to chemotherapy
  - Elderly/reduced GFR
  - Volume depletion

- Laboratory
  - Elevated LDH
  - Baseline hyperuricemia
  - Baseline renal dysfunction
Prophylaxis against TLS

• Aggressive hydration

• Prevent uric acid deposition into renal tubules
  • Urinary alkalinization
    • Target urine pH ≥ 7
  • Allopurinol
    • 300 mg daily to BID

• Rasburicase
Disseminated Intravascular Coagulopathy

Loss of normal hemostatic control in response to sustained and systemic cell injury
### Triggers of DIC

<table>
<thead>
<tr>
<th>Causes</th>
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<tbody>
<tr>
<td>- Sepsis/severe infection</td>
<td>- HELLP syndrome</td>
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<td>- Trauma/burn/heatstroke</td>
<td>- Vascular abnormalities</td>
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<tr>
<td>- Malignancy</td>
<td>- Kasabach-Merrit syndrome</td>
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<td>- Solid tumors</td>
<td>- Other vascular malformations</td>
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<td>- Acute leukemia</td>
<td>- Aortic aneurysms</td>
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<td>- Obstetrical conditions</td>
<td>- Severe allergic/toxic reactions</td>
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<td>- Amniotic fluid embolism</td>
<td>- Severe immunologic reactions (e.g., transfusion reaction)</td>
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<td>- Abruptio placentae</td>
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Relevance of DIC

- Microvascular thrombosis
- Organ dysfunction
- Bleeding
- Increased mortality
Management of DIC

= 

Treatment of underlying cause
Management of DIC

- Blood product support
  - Platelets in the bleeding patient if < $50 \times 10^9$/L
  - Fresh frozen plasma if bleeding and prolonged PT and PTT
  - Cryoprecipitate (2 pools) can be considered in patients with bleeding and fibrinogen levels less than 1.5 g/L

- Modulating profibrinolytic activity
  - Tranexamic acid

- Modulating thrombin generation
  - Heparin/LMWH
  - Antithrombin – controversial
  - APC – Prowess-SHOCK Trial showed no benefit
Hypercalcemia

- 20-30% of cancer patients
- Myeloma, lymphomas, cancers of prostate, lung, breast, and kidneys
Malignancy-Associated Hypercalcemia

Humoral Hypercalcemia
- PTHrP-related
- Non-PTHRP-related (including due to 1,25-vitamin D3)

Bone Invasion

Rare causes:
- Drug-related (retinoids)
- Immobilization
- PTH (parathyroid carcinoma)
Hypercalcemia: Symptoms

- N/V
- Constipation
- Decreased mental status
- Renal dysfunction
Treatment algorithm for malignancy-associated hypercalcemia.

Renal failure

Dialysis with low Ca++ bath

Hypercalcemia

Aggressive IV hydration

Volume overload

Loop diuretic

Lymphoma/Leukemia
Consider corticosteroids

IV Bisphosphonate +/- Calcitonin

Refractory Cases
Gallium nitrate or Denosumab

Mitchell H. Rosner, and Alan C. Dalkin CJASN 2012;7:1722-1729

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Thrombotic Thrombocytopenic Purpura

- Characterized by microangiopathic hemolytic anemia, thrombocytopenia, and microvascular thrombosis

- Mortality rate of TTP without treatment ~ 80-90%
Acquired TTP

- Usually occurs in older children and adults
- Secondary to IgG autoantibody against ADAMTS13
- May be idiopathic or associated with mitomycin C, cyclosporin, tacrolimus, quinine, ticlopidine, clopidogrel, TBI, allogeneic BMT, solid organ txpt, or pregnancy/postpartum state
• In the U.S., ~1000 new cases diagnosed per year

• Most patients range in age from 20-60

• Slight female predominance – 3:2

• Relapses occur in ~1/3 of those who achieve remissions.
Pathophysiology of TTP

- vWF
- ADAMTS13
- Inhibitor of ADAMTS13
ADAMTS13

- "A disintegrin and metalloprotease with eight thrombospondin type 1 repeats"
- #13 a family of 19 distinct ADAMTS enzymes identified to date
- Encoded on chromosome 9q34
- Produced by the liver
Normal release of vWF into circulation

Normal release of vWF into circulation

Stress!

Endothelial Cell

Weibel-Palade body

P selectin

Cleaved ULVWF Multimers 200 kd

ADAMTS13 cleaving protease

ADAMTS13 inhibitors: no cleavage of ULVWF

Endothelial Cell

P selectin

Weibel-Palade body

Stress!

TNF-alpha

histamine

IL-6

IL-8

ADAMTS13 inhibitors: no cleavage of ULVWF

Absence of ADAMTS13: ULvWF predominance

- ULvWF adheres to platelets and causes platelets to aggregate
- ULvWF has greater binding affinity to platelets than smaller vWF, possibly secondary to more effective exposure of gp1bα
- ULvWF may detach from endothelial cells in the presence of fluid shear stress/increasing torque generated by platelet adherence to ULvWF and embolize to downstream microvessels resulting in organ ischemia
## Classic TTP pentad

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<tbody>
<tr>
<td>1.</td>
<td>Neurologic abnormality</td>
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<td>2.</td>
<td>Renal failure</td>
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<td>3.</td>
<td>Thrombocytopenia</td>
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<td>4.</td>
<td>Microangiopathic hemolytic anemia (MAHA)</td>
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<td>5.</td>
<td>Fever</td>
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Laboratory Findings

- Thrombocytopenia (often <20K)
- Increased LDH secondary to lysis and diffuse organ ischemia
- RBC fragmentation (e.g. schistocytes and helmet cells) due to passage of RBCs through microvessels that are partially occluded by plt aggregates
Comparison of plasma exchange with plasma infusion in the treatment of TTP

Comparison of plasma exchange with plasma infusion in the treatment of TTP

Conclusions:

1. Plasma exchange is superior to plasma infusion in the treatment of TTP, both at the end of the first cycle of tx and after six months.

2. The significantly lower death rate when plasma is exchanged suggests a possible role for the removal of some plasma constituent in addition to the supply of fresh plasma.

Plasma Exchange

- **No defined schedule**
  - Performed on a daily basis until platelet count reaches ~150 (also monitor for normalization of Hb, LDH, and any clinical abnormalities at diagnosis), then taper
  - If response to initial treatment is poor, may need intensification of plasma volume exchange (1.5 vs. 1.0 or bid treatment) or initiation of immunosuppressive agents
Glucocorticoids

- Prednisone 1 mg/kg/d or Methylprednisolone 125 mg IV bid

- Suppresses production of ADAMTS13 autoantibodies by inducing lymphocytic apoptosis
Acquired HUS

- Occurs in 9-30% of children about a week after an episode of bloody diarrhea precipitated by ingestion of enterohemorrhagic bacteria that produce the shiga toxin (e.g. *e.coli* 0157:H7 and *shigella dysenteriae*)
- Sources include contaminated milk, cheese, or meat
- Common in Buenos Aires, Argentina, and Calgary, Canada

- Epithelial cells/monocytes release cytokines and chemokines.
- Endothelial cells secrete uLVWF and activate plts.

CH2------------------
glc gal gal

Shiga toxin

Globotriaosylceramide receptor
HUS - Treatment

- Plasma Exchange
- Supportive
  - IVF’s
  - RBC transfusions
  - Dialysis if appropriate
Atypical HUS

- Accounts for 5-10% of HUS
- Mortality rate ~50% vs 3-5% for typical, acquired HUS
- About 50% relapse, and over 33% require long-term dialysis; 16% who receive kidney allografts lose function of graft within 1 mo.

aHUS

- Due to a regulatory protein defect in the alternative complement pathway
- Results in excessive activation, endothelial damage, platelet activation, thrombus formation

Cell lysis
If suspicion for aHUS, begin plasma exchange but if no improvement after 3-5 days, may be unresponsive → eculizumab

Eculizumab

- Recombinant humanized monoclonal antibody that target C5
- Blocks cleavage of C5 and prevents formation of membrane attack complex
Hyperviscosity

- Increased serum viscosity resulting from increased serum Ig’s
- Waldenstrom’s macroglobulinemia/myeloma

- Symptoms
  - Typically occur when serum viscosity > 5 cp
  - Mucosal bleeding*
  - CNS symptoms
  - Cardiopulmonary symptoms
Effective short-term treatment for HVS in WM
A relatively small reduction in IgM concentration has a significant effect on lowering serum viscosity.
Bleeding is the most common sign of HVS
Urgent plasmapheresis should be carried out for patients experiencing visual symptoms to reduce the likelihood of blindness from retinal hemorrhages/retinal detachment.
Plasma exchange reduces plasma viscosity approximately 20% to 30% per session.
Major complications include pain and irreversible loss of neurologic function.

Goals of therapy:
- Pain control
- Preservation of neuro function
ESCC - Therapy

Symptomatic Tx
- Glucocorticoids
- Opioids
- Aggressive bowel regimen

Definitive Tx
- Assess spinal stability – Spine Instability Neoplasia Score
- Surgery -> RT
- +/- Chemotherapy
Superior vena cava syndrome
Typical clinical findings in a patient with superior vena cava syndrome

A: Plethora
B: Distended jugular veins
C: Cyanosis
D: Swelling hand/arm
E: Collateral circulation
F: Compression of SVC/tracheal compression
SVC syndrome - Mechanism

- SVC surrounded by relatively rigid structures (sternum, trachea, right bronchus, aorta)

- Extends ~6-8 cm, from inominate veins to right atrium

- SVC syndrome causes by neoplastic invasion of venous wall with associated thrombus or by extrinsic compression
• Prompts collateral venous return through:
  - Azygous venous system
  - Internal mammary venous system
  - Long thoracic venous system

• Develops in 5-10% of patients with right sided intrathoracic mass lesions

• Majority of cases due to bronchogenic cancer; 10-15% due to lymphoma

• Prognosis depends on underlying histology of tumor, presence of laryngeal and/or cerebral edema

• Symptoms often absent until obstruction near complete
  - Dyspnea
  - Facial and arm swelling
  - Chest pain
  - Dysphagia
  - Change in vision
  - Head fullness, headache
Treatment of SVC syndrome

Supportive
- Elevation of head
- Oxygen
- Corticosteroids
- Diuretics

Definitive Treatment
- Chemotherapy
- Radiation
- Stenting, particularly while bx being pursued
The End