ONCOLOGY EMERGENCIES

Cancer is the second leading cause of death in the United States with over 500,000 deaths annually. Despite improvements in survival and decreased prevalence of certain malignancies, the overall prevalence of cancer is expected to rise.

Efficient diagnosis and proper management of life-threatening complications may facilitate either definitive treatment of the underlying malignancy, palliation or at least improve quality of life.

Neutropenic Fever.

This can be caused by inflammation, transfusions, anti-neoplastic agents, antimicrobials and tumor necrosis. Whilst fever can be secondary to the malignancy itself, most fevers (55-70%) occur due to an infectious agent.

Neutropenia is defined as a absolute neutrophil count of < 1000 cells/mm^3 & is associated w/ a significant risk of infection & morbidity.

Febrile neutropenia is a medical emergency...

Clinical Features.

Fever is often the first and occasionally the only sign of infection in the neutropenic cancer patient, therefore a detailed history & physical examination is crucial.

Investigations.

Whilst antibiotic therapy is being started, each patient should have:

- FBC (w/ differential), electrolytes & coagulation studies.
- 2x peripheral blood cultures
- Urine culture & microscopy.
- Cultures from any indwelling lines.
- CXR (may be reserved only for patients w/ respiratory symptoms)

Differential Diagnoses.

- Approx. 85% of pathogens are bacterial (60-70% of which are Gram +ve).
- Reduction in Pseudomonas & other Gram -ve sepsis due to prophylactic antibiotic therapy whilst undergoing chemotherapy (usually Bactrim).
- Candida, aspergillus, cryptococcus & pneumocystis are also important infections to consider, as are viral infections such as HSV, VZV & CMV.

Management.

- Early antibiotic therapy: ***Piperacillin/Tazobactam (4.5 grams IV) q8h***
    - Frequency adjusted for renal function.
    - Addition of Gentamicin for severe sepsis.
    - Consider antivirals, antifungals etc (based on clinical picture).
- Early goal-directed therapy for sepsis.

- ***Vancomycin*** should be included for;
    - Clinically suspected catheter infections
    - Known colonisation of MRSA.
    - Positive blood cultures for Gram +ves (before final identification & susceptibilities has taken place).
    - Severe sepsis / Septic shock.
- Patients should be isolated w/ reverse barrier precautions in place.

Superior Vena Cava Syndrome.

Since the mid-20th century, malignancy has accounted for over 90% of cases of SVC syndrome. However, implantable intravenous (IV) devices (e.g., tunneled central lines, pacemaker leads) have increased the prevalence of thrombosis-related SVCS and now account for up to 40% of cases of SVCS.

- Confined by the chest wall and surrounding structures, a mediastinal mass impinging upon the SVC can easily obstruct blood flow.
- Over a period of 1–2 wks, the resultant high venous pressures and upstream vessel engorgement promote collateral vein dilatation to reduce this pressure.
- In diseases associated with pleural thickening and adherence of the surfaces (e.g., tuberculosis), bridging veins can develop across the pleural space producing significant systemic-to-pulmonary venous shunting and hypoxemia.

Signs & symptoms:

- Facial oedema (& conjunctival swelling) is the most common finding.
- Dyspnea at rest, cough, chest/shoulder pain, and hoarseness [more common in malignancy than benign conditions].
    - Result from direct effects of tumor compression or invasion of the airways or nerves.
- Neurological symptoms may result from raised venous pressure; but need to consider cerebral metastases.
- the *full-blown syndrome* manifests w/ thoracic & neck vein distention, facial plethora, upper limb oedema & cyanosis.

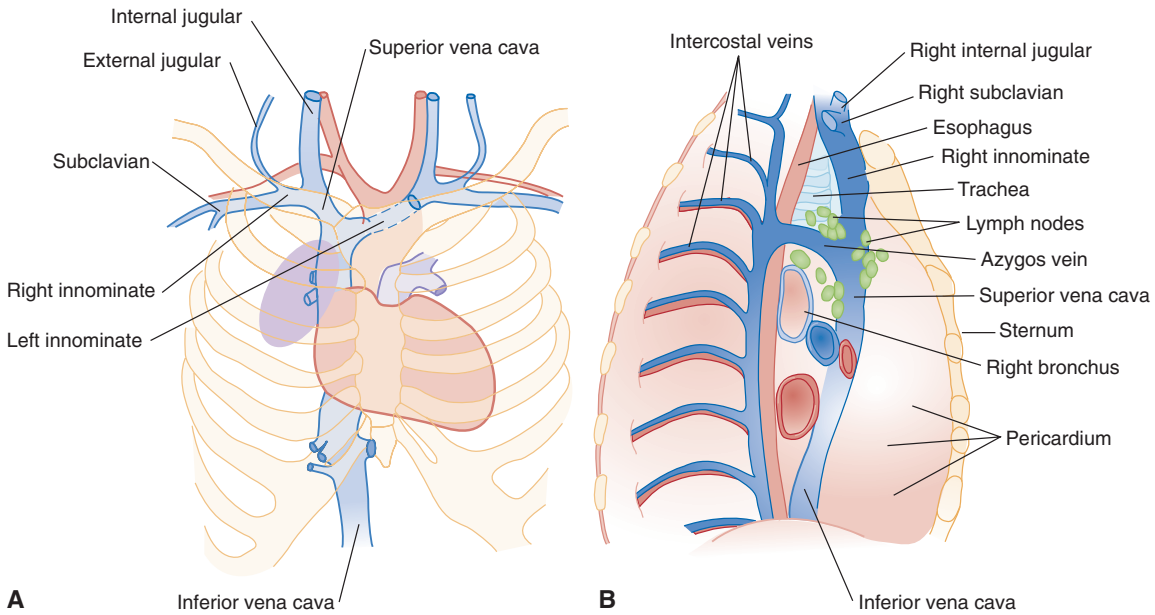


Figure 121-1. Frontal (**A**) and sagittal (**B**) sections of the thorax showing the relationship of the azygos vein to the superior vena cava (SVC), coalescence of innominates to form the SVC at the right second rib, and encasement of the SVC by nodal structures. Shaded area indicates classical site of obstruction. (From Lokich JL, Goodman R: Superior vena cava syndrome. JAMA 231:58, 1975.)

SVCS becomes a true emergency requiring empiric treatment only in the setting of airway obstruction (tracheal compression) or cerebral edema.

Investigations.

- *The differential diagnosis to exclude to pericardial tamponade.* (ie. ECHO !!)
- CXR may reveal a mediastinal mass (75% will be right-sided).

Management:

- Symptomatic relief
    - Elevate the head of the bed and supplemental oxygen are standard.
    - Diuretics may alleviate some swelling.
- Treatment of complications
- Therapy for the underlying condition.
    - Intravascular stunting can be used prior to tissue diagnosis.
    - Glucocorticosteroids are of unclear benefit (except in the cases of lymphoma or thymoma where indicated for the underlying malignancy).
    - Thrombosis-related SVC obstruction = anticoagulation, intravascular device removal, and balloon dilatation or stenting if significant fibrosis remains.
    - Chemotherapy & radiotherapy may be used for SCLC & lymphoma.

Median survival of patients with cancer-induced SVCS is ~6 months after presentation, but many patients have survived over 2 yrs with treatment.

Malignant Pericardial Disease.

Pericardial effusion is common in malignancy with up to 34% of cancer patients having involvement of pericardium. Whilst neoplastic etiology is reported in 7% of all acute pericardial disease, [and in ~50% of these cases it was the first manifestation of previously undiagnosed malignancy]; tamponade resulting from neoplasm is *uncommon.*

Most malignant pericardial disease is due to metastasis from sites of disease outside of the heart and pericardium, primarily from lung, breast, and hematologic sources. It can also result from radiation-induced pericarditis, fibrosis etc (which can lead to constrictive pericarditis).

Pathophysiology:

- Normal pericardial space contains < 50mL of fluid.
- Fluid filling the pericardial sac initially has a flat pressure response until reaching the pericardial reserve volume, i.e., the volume that begins to distend the pericardium.
- Pressure then begins to rise abruptly due to the relative inextensibility of the parietal pericardium.
- The steep rise in pressure with minimal increment in pericardial fluid volume eventually leads to a critical intra-pericardial pressure, which in turn results in impaired filling of the cardiac chambers and hemodynamic compromise.
- The amount of the pericardial fluid that causes tamponade is related to the rate of fluid formation.

Signs & symptoms.

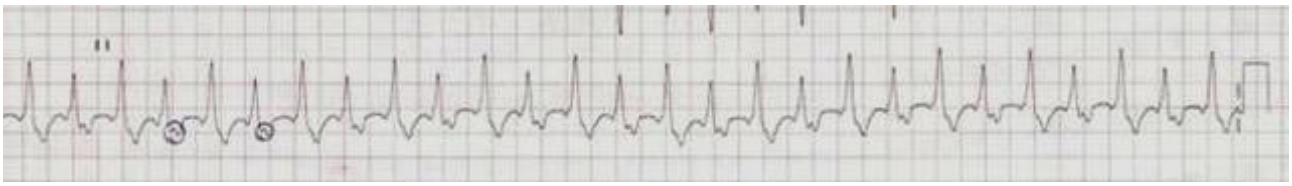
- Exertional dyspnea is the most common presenting symptom.
- Pulsus paradoxus is the most common sign (~30% of presentations of malignant pericardial effusion and 77% of cases of acute tamponade).
- Tachycardia is common.
- There may be extreme anxiety and apprehension.
- Pallor, diaphoresis & altered mental state in severe cases.
- Beck's Triad [hypotension, raised JVP & muffled heart sounds] is more common in rapidly accumulating fluid & acute tamponade (compared to chronic tamponade).

Investigations:

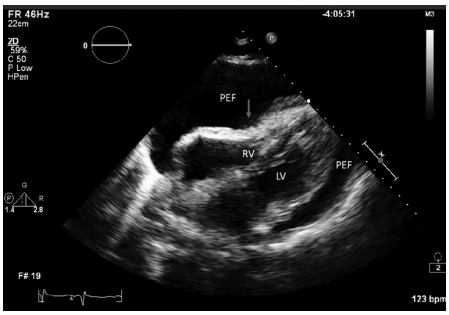
- <u>CXR.</u>
  - Enlarged cardiac silhouette.
  - Increased transverse diameter.
  - Clear lung fields / Normal vasculature.

<u>Invasive cardiac monitoring.</u>
Demonstrates elevated and equalized right atrial, right ventricular diastolic, and pulmonary arterial occlusion pressures reflecting tamponade physiology

- <u>ECG.</u>
  - Low-amplitude QRS
  - Non-specific ST-T wave changes.
  - Electrical alternans *(below)*



- <u>ECHO.</u>
  - Diagnostic tool of choice
  - Defines the size & location of the effusion
  - Demonstrates hemodynamic significance
  - Guides pericardiocentesis



RA & RV diastolic collapse = tamponade

Treatment.

- Volume resuscitation.
  - Cautious fluids, as hypervolaemia may be detrimental.
- Bedside emergency pericardiocentesis.
  - Leaving drain in-situ is preferable as fluid will re-accumulate.
- Surgical referral for pericardial window.

Malignant Spinal Cord Compression.

Malignant spinal cord compression occurs in ~5% of terminal cancer patients within the last 2 years of life. Despite a median survival of <6 months following diagnosis, prompt treatment usually palliates pain and prevents paralysis.

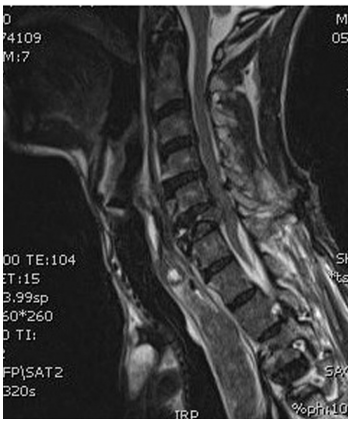
Most malignant cord compression is epidural in origin.
- Intramedullary (intradural) and leptomeningeal (dural) malignancy are rare.

The development and location of vertebral metastases correlate with;
- degree of vertebral blood flow
- the affinity for bone
- anatomic location of the tumor

The three most common malignancies w/ affinity for bone are;
1. lung
2. breast
3. prostate.

Multiple Myeloma, Non-Hodgkin's & RCC can also cause bony disease.

Signs & symptoms.
- Back pain is the first symptom in > 95% of malignant spinal cord compressions.
- 40-90% of affected individuals experience sensory abnormalities that correspond to nerve roots w/in 4 levels below (& two above) their compressed cord.
  - 75% have focal weakness.
- 50% have bowel or bladder dysfunction
- Look for symmetrical weakness w/ flaccidity or hyporeflexia
  - Spasticity & hypertonia occur later.



Investigations.
- Post-void residuals suggest cauda-equina syndrome.
  - Sn 90%, Sp 95%.
- MRI is *gold-standard.*
  - Entire spine should undergo T1 & T2 weighted imaging (1/3 of cases have multiple sites of metastases).
- Plain x-ray is abnormal in 70-90% of cases.
- CT may be helpful, as may Bone scan.

Management.
- Rapid treatment improves short-term prognosis.
- Corticosteroids mitigate vasogenic oedema (usu. high dose dexamethasone).
  - Recommended for pt's w/ abnormal neuro exam.
- Radiotherapy is fundamental. *(Involve Radiation Oncology early).*
- There may be a role for surgical decompression (*Neurosurgery*).

Table 1. Radiosensitivity of tumors

Sensitive
Lymphoma
Myeloma
Breast
Prostate
Small-cell lung cancers
Resistant
Melanoma
Sarcoma
Renal cell carcinoma

Table 3. Indications for surgery (71)

Spinal instability (e.g., spinal deformity, bony retropulsion into canal, pathologic fractures)
Previous radiation therapy to area
Disease progression despite radiation
Radioresistant tumor
Unknown primary tumor
Paraplegia for <48 hrs
Single area of cord compression

Malignancy-Associated Hypercalcaemia.

Malignancy-associated hypercalcaemia (MAH) occurs in 25% of cancer patients & accounts for 1 in 3 hypercalcaemic presentations to the ED. Anti-hypercalcaemic treatment *does not improve mortality* & 50% die within a month of diagnosis.

Recall that calcium homeostasis is maintained by a balance in intestinal absorption, bone resorption & renal excretion. *Parathyroid hormone (PTH)* modulates Ca^{2+} by increasing bone resorption & promoting renal re-absorption (& phosphate excretion). *Calcitriol* promotes intestinal Ca^{2+} absorption + mild bone resorption.

MAH results from;

1. PTH-related protein-induced humoral hypercalcaemia
2. local osteolysis (from bony metastases)
3. lymphoma-associated calcitriol production.
4. ectopic PTH secretion.

This mechanism varies between malignancies...

Signs & symptoms.

- Non-specific: lethargy, confusion, constipation, hypovolaemia & dysrhythmias.
- Clinical effects are related more to the rate of rise, not the absolute concentration.

BOX 121-7 Common Signs and Symptoms of Hypercalcemia in Malignancy

General
Itching

Neurologic
Fatigue, muscle weakness, hyporeflexia, lethargy, apathy, disturbances of perception and behavior, stupor, coma

Renal
Polyuria, polydipsia, renal insufficiency

Gastrointestinal
Anorexia, nausea, vomiting, constipation, abdominal pain

Cardiovascular
Hypertension, dysrhythmias, digitalis sensitivity

Investigations.

- Electrolytes (particularly Phosphate, Magnesium & Potassium).
- Serum PTH & PTH-related protein.
- ECG:
    - prolonged PR interval
    - widened QRS
    - shortened QT interval.
    - Others: BBB or Brugada pattern. Bradydysrhythmias.

Management.

- Restoring intravascular volume is fundamental.
    - N.Saline is recommended, targeting a urine output of 100-150mL/hr.
    - Will only result in a modest decrease.
- Bisphosphonates (*palmidronate, zoledronic acid).*
    - First line therapy. Palmidronate 90mg IV over 4-24 hours.
- Loop diuretics:
    - Whilst they inhibit Ca^{2+} resorption in the loop of Henle they potentially can worsen the other electrolytes...
    - Best reserved for those with fluid overload.
- Haemodialysis - for CCF, severe AKI & significant neurological changes.
- Calcitonin: whilst it has rapid onset; is mostly abandoned now.

Acute Tumour Lysis Syndrome.

A potentially life-threatening emergency characterised by a constellation of metabolic derangements resulting from the death of malignant cells & release of their intracellular contents. It is primarily associated with aggressive haematological malignancies due to the large cell burden & rapid cell lysis with treatment.

Almost all types of cancer therapy can cause TLS, including systemic chemotherapy, intrathecal MTX, steroids, biological agents, radiotherapy & tamoxifen.

The metabolic derangements are included in the table below...

Table 5. Metabolic abnormalities in acute tumor lysis syndrome (115, 124, 126)

Metabolic Abnormality	Value or Change From Baseline[124a]	Clinical Implications	Management
Hyperkalemia	≥6.0 mmol/L or 6 mEq/dL or 25% increase	Muscle cramps Paresthesias Dysrhythmias Ventricular fibrillation Cardiac arrest	Polystyrene sulfonate 1 gm/kg Insulin 0.1 unit/kg with dextrose 25% 2 mL/kg Sodium bicarbonate 1–2 mEq/kg IV push Calcium gluconate 100–200 mg/kg slow IV infusion
Hyperphosphatemia	≥2.1 mmol/L for children or ≥1.45 mmol/L for adults or 25% increase	Nausea Vomiting Diarrhea Lethargy Seizures Acute kidney injury	Volume loading Removal of phosphate from IV fluids Oral phosphate binders Hemodialysis
Hypercalcemia	≤1.75 mmol/L or 25% decrease	Muscle cramps Tetany Hypotension Dysrhythmia	Calcium gluconate 50–100 mg/kg slow IV infusion with electrocardiogram monitoring. Give only if symptomatic.
Hyperuricemia	≥476 μmol/L or 8 mg/dL or 25% increase	Acute kidney injury	Volume loading Rasburicase (see text for dosing) Allopurinol by mouth or IV

- Hyperkalaemia is the most serious of the acute TLS manifestations & occurs 6-72 hours post initiation of anti-tumour therapy. Obviously exacerbated by AKI.
- Malignant cells contain up to 4x the amount of inorganic phosphorus than normal cells.
    - Chemotherapy prevents reutilisation of phosphate.
    - Results in hypocalcaemia (from binding to excess phosphate).
- AKI can be exacerbated by obstructive uropathy (secondary to calcium phosphate crystals).
- Hyperuricaemia can result in uric-acid crystal precipitation in renal tubules.
    - Again, potentiating obstructive uropathy & AKI.

The risk of TLS increases with the bulk of the tumour, with the presence of hyperuricaemia or with renal impairment (prior to anti-tumour therapy). Other risk factors are included below...

BOX 121-4 Risk Factors for Acute Tumor Lysis Syndrome

Increased lactate dehydrogenase levels (>1500 U/L)
Advanced disease with abdominal involvement
Preexisting renal dysfunction
Post-treatment renal failure
Acidic urine
Concentrated urine
Preexisting volume depletion
Young age

Clinical Features.

- Symptoms are related to the underlying malignancy & the electrolyte imbalances. (*See table on previous page...*)

Management.

"Its easier to stay out of trouble than get out of trouble"

The main principles of TLS management are:

1. identification of high-risk patients @ initiation of therapy.
2. early recognition of metabolic & renal complications
    - prompt supportive care and early haemodialysis.
    -

More thoroughly....

- Prophylactic measures to prevent AKI.
    - Volume loading ++ (the single most important intervention).
    - Enhances renal blood flow, GFR, urinary volume.
    - Alkalinising urine is *no longer supported* ... (risk of worsening nephropathy).
- Hyperkalaemia is treated as usual.
- Hyperphosphataemia is treated w/ volume loadings & phosphate binders.
    - Renal replacement therapy may be required.
- *Rasburicase* (recombinant urate oxidase): breaks down uric acid to more soluble forms. It is highly effective at rapidly normalising levels. (better than allopurinol).
    - Can cause haemolytic anaemia & methaemoglobinaemia (in patients w/ G6PD deficiency).
    - Dose = 0.2mg/kg IV daily, for 5 days.
- Allopurinol prevents formation of uric acid (inhibiting xanthine oxidase).
    - Typically started *prior* to chemotherapy.
    - Hypersensitivity ++
    - Does *not* clear already formed uric acid.
- Renal replacement therapy
    - acute TLS w/ significant AKI
    - poor response to medical therapy
    - symptomatic life-threatening metabolic derangements.

BOX 121-5 CRITERIA FOR INSTITUTING HEMODIALYSIS

Serum potassium 6 mEq (6 mmol/L)
Serum uric acid 10 mg/dL (590 mol/L)
Serum creatinine 10 mg/dL (880 mol/L)
Serum phosphorus 10 mg/dL (phosphate 3.2 mmol/L) or rapidly rising
To reduce volume overload
Symptomatic hypocalcemia

Hyperviscosity Syndrome.

HVS refers to the clinical sequelae of increased blood viscosity. This results from excessive elevations in certain paraproteins (immunoglobulins) or cellular blood components (WBC, RBC or thrombocytosis) and causes significant sludging, decreased perfusion of microcirculation & vascular stasis (especially CNS, retina & cardiopulmonary circulation).

Pathophysiology.

- Most commonly associated w/ plasma cell dyscrasias (paraproteinaemias).
    - Waldenstrom's macroglobulinaemia is the most common cause.
    - Also: MM, cryglobulinaemia and leukaemias (particularly in the blastic phase / blast crisis).

Clinical Features.

- A symptomatic triad:
    1. mucosal bleeding
    2. visual disturbances
    3. neurological manifestations

  a 'classic' presentation...
- Visual disturbances (even visual loss) may occur w/ retinopathy appearing as *venous engorgement*, microaneurysms, haemorrhages & exudates.
- Nasal, GIT and surgical site bleeding occurs with normal coagulation profile and PLT count.
- Neurological signs include dizziness, headaches, seizures, drowsiness (decreased LOC) etc...
- Cardiorespiratory symptoms: respiratory distress/failure, hypoxia, CCF, infarction.
- Constitutional symptoms: fatigue, anorexia, weight loss.

Investigations.

- Include FBC, coagulation profile, renal function & electrolytes.
- KEY may lie in blood sample repeatedly clotting in the lab equipment.

Management.

- Plasmapheresis !! (consult ICU & Haem/Onc early if suspected).
- Temporising measures include:
    - Hydration ++
    - Diuresis.

Other Oncology Emergencies To Know About...(but covered elsewhere).

- Seizures
- Cerebral Herniation
- CNS Infections

References.

1. Rosen's Emergency Medicine. Concepts and Clinical Approach. 7th Edition
2. McCurdy, M. T., & Shanholtz, C. B. (2012). Oncologic emergencies. Critical Care Medicine, 40(7), 2212–2222.