# Oncologic Emergencies

By Paul Zito

# Oncological Emergencies

- Treatment and consultation emergently. Call Oncology any time of night for discussion.

- Acute Leukemia/Burkitt Lymphoma
- SVC Syndrome/Spinal Cord Compression
- Tumor Lysis Syndrome
- TTP/HUS
- Neutropenic Fever
- Thrombocytopenia/ITP

# Oncologic Urgencies

- Hyperviscosity
- Hemolysis
- Aggressive Lymphoma – CNS/Mediastinal/DLBCL/Richter's Transformation.
  - Can have presenting issues which present more emergently.
- Most cases of Acute Leukemia.
- HLH

Please call us with questions whenever these are suspected or seen so we can advise expediated workup and treatment.

# Case 1

- 62 year old Female
  - Presented to ER in regional hospital with bruising, fatigue.
  - Found to be pancytopenic with thrombocytopenia
- Coagulopathy and labs consistent with DIC
- Blasts noted on peripheral blood.
- Bone marrow biopsy performed and transfer requested to tertiary center
- Fell at outside hospital during this time and sustained a periorbital hematoma.
- Biopsy C/W APML

# Case Continued.

- Arrived 24-48 hours later
- Worsening DIC
- Commenced on ATRA and Arsenic trioxide + Chemotherapy

- Improving counts 24 hours later.
- Requiring frequent platelet transfusions.
- Platelets count = 1 around 48 hours after arrival.
- Developed AMS.
- CT Head at 2 AM revealed catastrophic ICH with herniation.

# Acute Leukemia/Burkitt Lymphoma/Mediastinal Lymphoma

Included in emergencies as prompt consultation with Oncology needed as soon as suspected to avoid delays in diagnosis and treatment.

- AML, ALL and Burkitt lymphoma will all present differently.
- AML, ALL indistinguishable in early phase. Patient will present with cytopenias, commonly pancytopenic. Blasts on peripheral blood.
- Needs flow cytometry on peripheral blood, bone marrow biopsy. Supportive transfusions to avoid bleeding.
- DIC workup needed. If signs of DIC then patient may have APML. Patients can get sick very quickly. Needs evaluation and prompt initiation of ATRA.

# Burkitt Lymphoma

Aggressive B Cell Lymphoma.  High proliferative index, Ki67.

Typical immunophenotype: sIg+, CD10+, CD20+, TdT-, Ki-67+ (≥95%), BCL2-, BCL6+

Most common karyotype is MYC rearrangement as a sole abnormality. There is an uncommon variant of BL without MYC rearrangement but with 11q aberration.

Can had peripheral blood leukemic presentation

Rapid growth.  Doubling in size every few days.

Can have spontaneous tumor lysis and lactic acidosis.

Rapid biopsy and workup needed.  Keep inpatient to start chemotherapy.

Suspect in any younger person with history of mass enlarging over a number of weeks.

# Quick case:

- 24 year old security guard from regional town.  Noticed 2-3 weeks for worsening jaw pain.
- Dental examination and antibiotics provided without relief.
- 2 weeks later presents to ER with B symptoms, fevers, chills, sweats.
- Pancytopenia with blasts on peripheral blood.
- Severe lactic acidosis with dyspnea.
- Small cutaneous nodules and ongoing jaw pain.

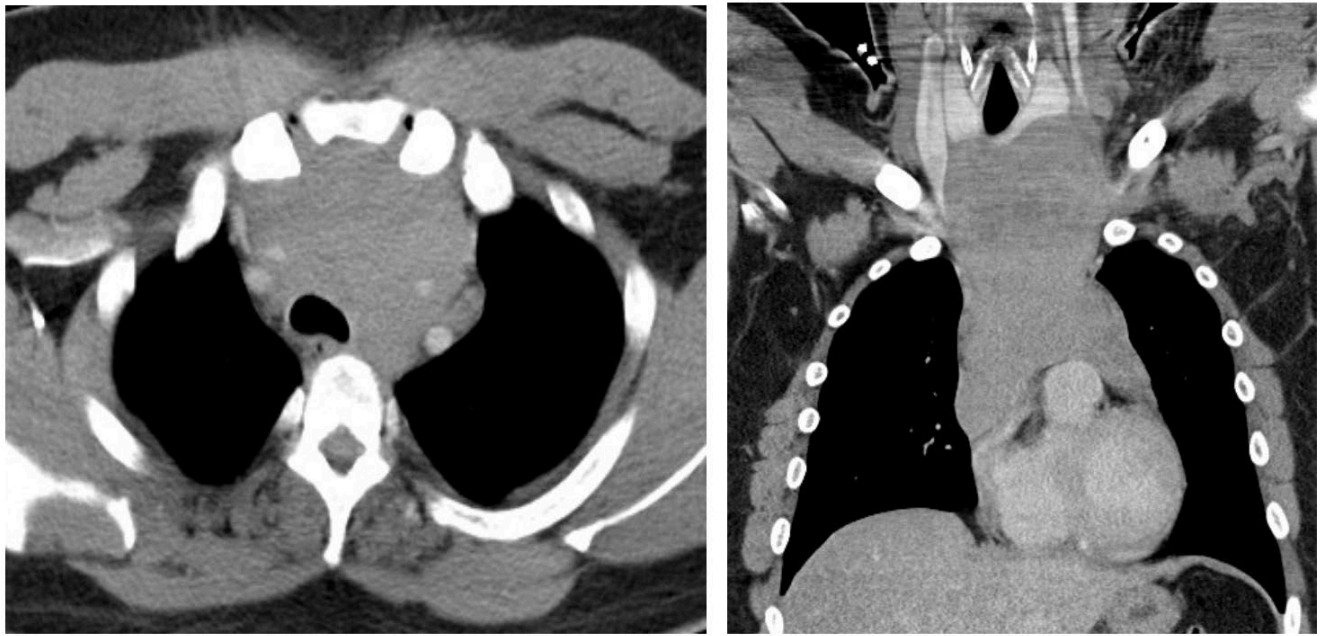
- Bone marrow, skin lesion biopsy and flow cytometry sent asap.
- Flow cytometry showed B Cell process concerning for Burkitt Lymphoma.
- Commenced steroids and chemo ASAP.

# T Cell ALL and T-cell lymphoblastic leukemia (LBL)leukemia

- T-cell ALL is when there is extensive bone marrow involvement
- T-cell LBL is preferred when there is primarily a mass lesion with < 20-25% blasts in the marrow
- T-ALL frequently present with a high tumor burden with hyperleukocytosis and large mediastinal masses.
- Highly aggressive disease but potentially curable with 5 yr OS rates compared to B-ALL (48%-41%)

# T Cell ALL with Mediastinal Mass

(aka T-Lymphoblastic Lymphoma)



## SVC Syndrome

Tumor encasement and compression or invasion of superior vena cava.

Venous catheter associated thrombosis also a potential cause.

Causes venous stasis and congestion in head and neck.

Signs and Symptoms:

- Facial plethora
- Choking feeling
- Pemberton's Sign
- Upper extremity edema
- Venous collaterals upper chest.

Oncologic Causes:

NSCLC, SCLC, Hodgkin's Lymphoma, Non Hodgkin's B and T Cell lymphomas, Primary Mediastinal Lymphoma, Germ Cell Tumors, Anaplastic Thyroid.

# Spinal Cord Compression

Spinal Cord Compromise is always a neurological and oncological emergency.

Can be caused by any extrinsic compression of spinal cord.

Common oncologic causes include an array of solid and hematological malignancies.

- Small Cell, RCC, Prostate, Breast, NSCLC.
- Lymphoma, Myeloma, Plasmacytoma.

Always perform prompt imaging on a patient with new onset back pain and extremity weakness.

Careful history and physical exam including reflexes, tone to identify likely site.

# Case 2

- 68-year-old gentleman who had noticed a metallic taste in his mouth and decreased appetite around 6 to 8 weeks prior. Seen by primary care for labs revealing elevated alk phos. Received an ultrasound of the gallbladder which was negative. Continues to workout when following a workout he noticed developing back pain and lower extremity numbness. Over the period of a number of hours he developed rapid onset bilateral lower extremity weakness.

- MRI of C-spine revealed metastatic disease in the vertebral bodies noted on C5-C7. MRI lumbar spine revealed diffuse osseous metastatic disease involving all visualized thoracic and lumbar vertebral bodies sacrum and pelvis.

- T7 suspicious for tiny dural metastatic lesion. Edema and cord 3 thoracic cord and conus at T10-T12 level.

# Case Continued

- Noted to have dural/epidural enhancement and involvement of the spinal cord. Presentation of acute onset of paralysis consistent with spinal cord infarction.
- Workup including biopsies ordered. PSA noted to be 854.
- Flaccid Paralysis  continued.
- Commenced on Casodex inpatient.
- Neurosurgery consulted without appropriate lesion for decompression
- Commenced on androgen deprivation.
- Patient continues to be seen in clinic has had some resolution of neurologic function and is now able to walk with a frame.

# SVC Syndrome or Cord Compression Treatment:

- Tissue Diagnosis ASAP in both cases
- Consult IR for stenting of SVC.
- Anticoagulation if thrombosis or risk for thrombosis.
- Steroids if lymphoma once biopsy obtained. Usually Pred 1mg/kg or Dexamethasone 4-6mg QID.
- Consult Neurosurgery for cord decompression and biopsy at same time.
- Solid tumor diagnosis.  Start treatment ASAP. Chemotherapy may need to be delayed pending wound healing from decompression surgery..
- Consult Rad Onc for radiation in either case.

# Case 3.

- 67 year old male with history of hypertension, peripheral artery disease, previous smoker who quit last year, who presents for evaluation of fatigue, diarrhea, abdominal pain, back pain.
- The patient had symptoms of COVID 19 for the previous 11 days. He completed a Z-Pak, and was on Paxlovid. He had not been able to keep anything down for the previous 3 days due to nausea and vomiting. He reported a migraine, and he was tender to palpation of his abdomen.

- CBC – WBC 4.4, Hb 14.5, Plt 237. ANC 2400, ALC 1400, No blasts.
- CMP – BUN 85, Cr 2.26, CO2 8, Cl 101, Na 126, K 5.0, Ca 8.2, TP 6.6, Alb 3.0, LDH 282.
- HCV Ab Reactive. Folate 6.3, B12 870
- Lactic Acid 3.1
- Uric Acid 13.9

# CT Scan

- Large left pleural fluid. Small right pleural fluid.  Left lung consolidation with probable atelectasis. Small patchy groundglass pneumonitis of the lungs bilaterally, right greater than left.
- Mild sclerosis of the sternal manubrium. Possible osseous metastatic disease. Further evaluation with whole-body bone scan recommended.
- Edema or mild prominent retrocrural lymph nodes, right greater than left.
- Mild splenomegaly.
- Left periaortic lymphadenopathy or varices.
- Soft tissue density felt to be bowel at the left retroperitoneum adjacent inferolateral left kidney. Differential included retroperitoneal mass, lymphadenopathy, peripheral left renal mass, and small subacute retroperitoneal hematoma.
- Abnormal left pelvic side wall thickening with soft tissue infiltration, lymphadenopathy, or subacute appearing pelvic hematoma. This measured up to 2.5 cm in thickness.
- Bilateral pelvocaliectasis of the kidneys suggesting bilateral renal obstruction, left greater than right.
- Possible mild colitis of the sigmoid colon.

# Clinical Case Continued

- Urology consulted for cystoscopy and stenting.
- Core biopsy of lymph node obtained.
- Worsening renal impairment
- Uric acid not addressed.
- Worsening lactic acidosis.
- Oncology consulted once biopsy returns 5-6 days later.

# Emergencies - Tumor Lysis Syndrome

- Classic tetrad of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia.
- Risk assessment and prophylactic therapy is critical in preventing this oncological emergency.
- Treatment of established TLS involves aggressive hydration, electrolyte management, and the use of hypouricemic agents.

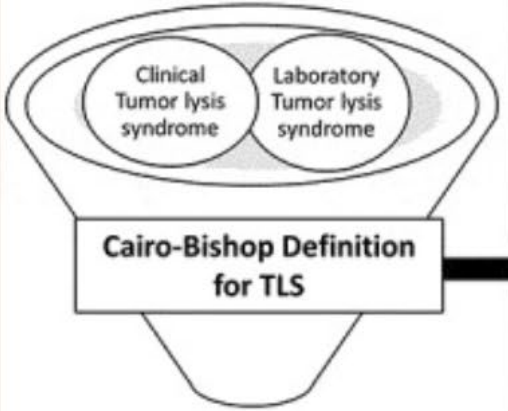
# Pathophysiology

- Tumor lysis releases cell contents.
- Intracellular Potassium release results in hyperkalemia
- Phosphorus release results in calcium phosphorus precipitation and hypocalcemia.
- DNA release cause hyperuricemia and acute renal impairment + gout.

- Results.  Acute Renal Failure, Cardiac Arrythmia.

High risk of Tumor lysis syndrome

- Burkitt leukemia
- Burkitt Lymphoma with ↑ LDH
- ALL with WBC count≥ 100,000/µL
- AML with WBC count ≥100,000/µL
- Lymphoblastic Lymphoma with ↑ LDH
- T-cell leukemia/lymphoma, Diffuse large B-cell lymphoma, transformed lymphoma with↑ LDH & bulky tumor
- Mantle cell lymphoma with ↑ LDH & bulky tumor
- Childhood diffuse large B-cell lymphoma ↑ LDH
- CLL treated with venetoclax/ ↑ LN/ ↑ UA/ ↑ Lymphocyte count




**Intrinsic tumor-related risk factors**

- High cell proliferation rate
- High risk cancers (see insert)
- Large tumor burden/bulky disease (>10 cm)
- Chemosensitivity

**Patient-related risk factors**

- Pretreatment hyperuricemia or hyperphosphatemia
- Pre-existing nephropathy
- Oliguria/acidic urine/nephrotoxins
- Inadequate hydration

## Tumor Lysis syndrome (TLS)

### Laboratory TLS

**2 or more of the following laboratory abnormalities within 3 days prior to and up to 7 days after initiation of cytotoxic therapy:**

**Uric acid ≥8 mg/dL**

**Potassium ≥6 mEq/L**

**Phosphate ≥6.5 mg/dL (children)**

**Phosphate ≥4.5 mg/dL (adults)**

**Calcium ≤7 mg/dL**

**OR**

**25% change from baseline in any of the above analytes**

### Clinical TLS

**Laboratory TLS plus 1 or more of the following:**

**Creatinine 1.5 times the upper limit of normal**

**Cardiac arrhythmia**

**Seizure**

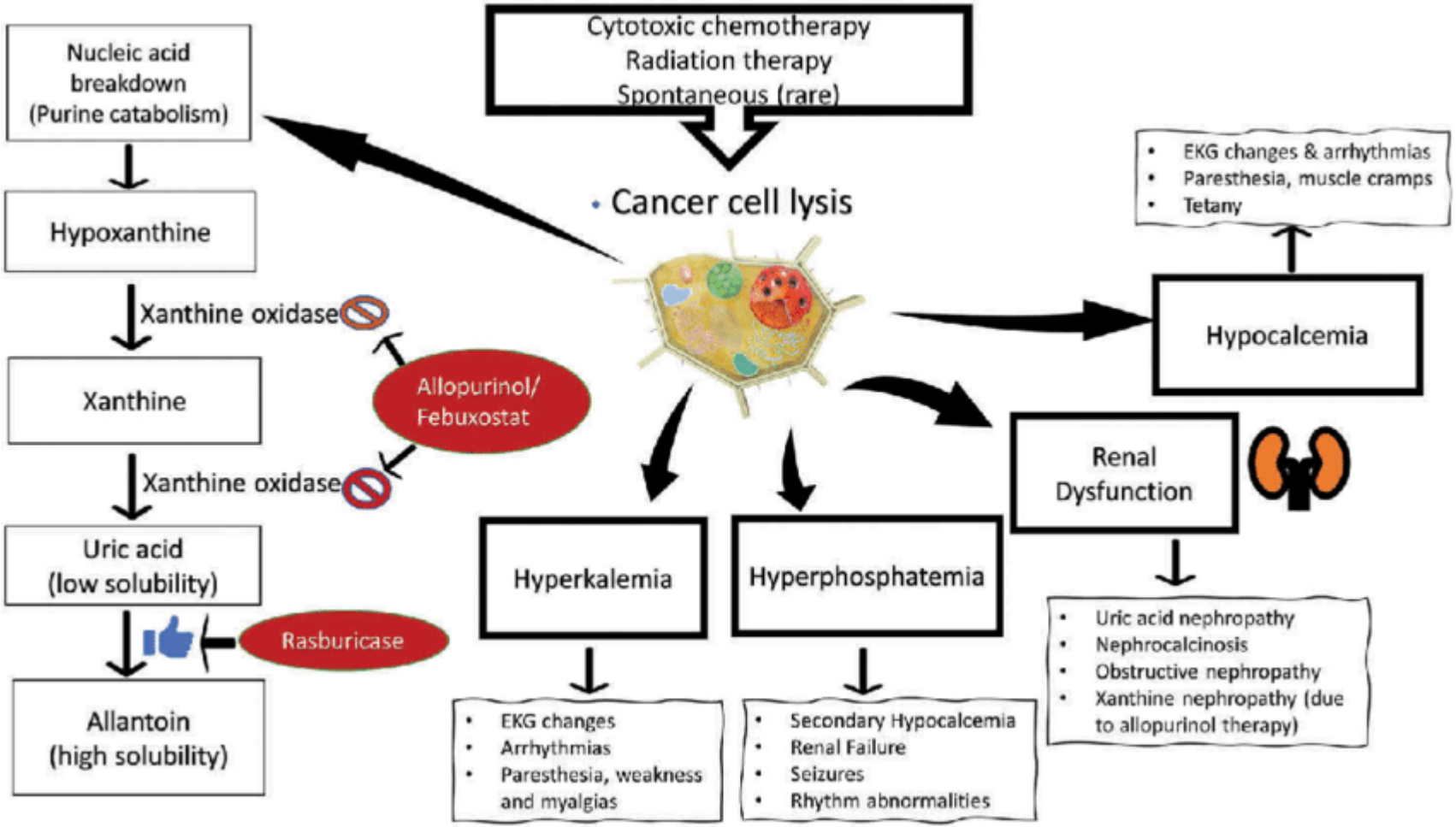
**Sudden death**

# Case Continued

- Lymph node, core biopsy:
  - Diffuse large B-cell lymphoma, germinal center B-cell type.
- Oncology consulted. No Rasburicase on formulary at institution -> transferred.
- Given rasburicase and TLS management.
- Unstable. Commenced on Prednisone and Rituximab.
- Once condition stabilized commenced Mini-R-CHOP.
- Improvement of all derangements over next few days.
- Completed 6 cycles R-CHOP outpatient.
- Currently in remission.

# TLS

- May occur in variety of solid and hematological malignancies.
- ALL, AML, CLL/SLL, Diffuse Large B Cell, Burkitt, T Cell Lymphoma, Primary Mediastinal Lymphoma, Plasma Cell Leukemia.
- Some solid tumors with high tumor burden such a metastatic breast, NSCLC, Small Cell.
- Any time there is large tumor bulk and cell lysis.
- Always check Calcium, Uric Acid, Creatinine, Potassium, Phosphorus in patients with bulky disease.
- May occur spontaneously or more commonly shortly after commencing chemotherapy




https://www.researchgate.net/figure/Pathophysiology-and-clinical-manifestations-of-Tumor-Lysis-Syndrome_fig2_342174192/download?_tp=eyJjb250ZXh0Ijp7ImZpcnN0UGFnZSI6Il9kaXJlY3QiLCJwYWdlIjoiX2RpcmVjdCJ9fQ

# Treatment of TLS

- Regular labs, every 4-6 hours.
- Good IV access. PICC, Port, multiple IVs at least.
- Fluids.
- Cardiac Monitoring and Urine output
- Correction of electrolyte abnormalities.
- Potassium - Insulin, Dex, Kayexalate. If needed dialysis. Aggressive and frequent.
- Hypocalcemia – if symptomatic lowest dose required to reduce symptoms. Oral Phosphate binders.
- Hyperuricemia. Start Allopurinol before chemotherapy in high risk patients. Continue until TLS resolved.
- Rasburicase promptly. If unavailable at your institution then transfer to higher level care.
- Dialysis may be necessary.

# Duration of TLS

- Usually worst in first 24-48 hrs after initiation of treatment
- After this can usually decrease blood draw frequency.
- Note:
- Venetoclax is BCL2 inhibitor known to cause significant tumor lysis when used.  All hematological malignancy but even CLL/SLL with large volume disease.
- Can occur with each dose increase.

# Case 4

- Previously healthy 63-year-old woman presented to the emergency department with spontaneous purpura without other symptoms.
- The physical examination was normal, except for the purpura.
- The hemoglobin level was 11.6 g per deciliter, and the platelet count was 14,000 per microliter.
- The initial diagnosis was primary immune thrombocytopenia, and treatment was begun with dexamethasone.
- Day 2 laboratory data suggested the diagnosis of TTP, with a haptoglobin level of less than 30 mg per deciliter, negative results on a direct antiglobulin test, a creatinine level of 0.8 mg per deciliter (71 µmol per liter), and a lactate dehydrogenase level of 605 U per liter.
- On day 4, a low level (<5%) of the enzyme ADAMTS13 confirmed the diagnosis of TTP. The patient declined to undergo plasma exchange and was treated with glucocorticoids, rituximab, and antihemophilic factor VIII

# TTP/HUS

- TTP, HUS and Complement mediated (atypical) HUS are clinically similar disorders that are associated with microangiopathic hemolytic anemia (MAHA), thrombocytopenia and microvascular thrombosis.
- When neurologic impairment is present the patient is more likely to be classified TTP
- Acute renal failure is the hallmark of HUS
- In some cases there is significant overlap.
- Atypical HUS tends to have no diarrhea but evidence of renal impairment

# TTP Brief History

- 1924: First case described by Moschcowitz. *(1955: first case of HUS described)*. Otherwise, these diseases remained mysterious until…
- 1982: "unusually large" multimers of vWF found to accumulate in plasma of patients with TTP. *(1985: typical HUS linked to enterohemorrhagic E.coli)*.
- 1991: Rock et al proved that *plasma exchange improved mortality to ~10-20% (formerly 90%).*
- 1998: TTP pathophysiology linked to ADAMTS-13 deficiency (though not 100% association).

# TTP

- Annual incidence: 4-11 cases per million people.
- Etiologies:
- Mostly idiopathic (38%) – higher incidence in females, obese, African Americans.
- Estrogen Use
- Autoimmune (13%).
- Drug-associated (13%) - quinine, ticlopidine, clopidogrel, cyclosporine.
- Pregnancy-induced (5%).
- HSCT** (3.5%).
- Malignancy
- HIV, Pneumococcal, E.coli 0157:H7
- Survival with plasma exchange: 78 -83% (including patients with renal failure).

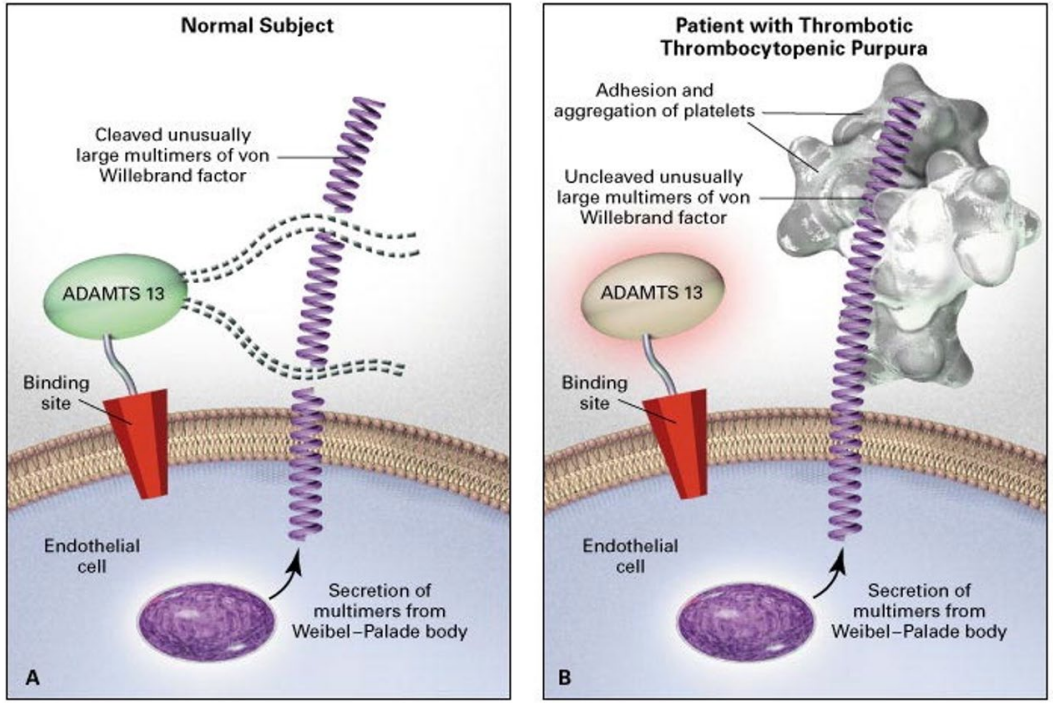
# Conditions that Mimic and Must Consider

- HELLP/pre-eclampsia
- Autoimmune (with alternate mechanism) – eg. SLE nephritis, acute scleroderma, APLA, Evan's syndrome, vasculitis.
- DIC
- HUS – mostly associated with Shiga toxin producing E.coli
- Systemic infection: can cause thrombocytopenia and MAHA without DIC. High fevers make it less likely to be TTP.
- Systemic malignancy – most notably breast and gastric adenocarcinoma.
- Malignant hypertension

# Pathophysiology

- Acquired antibodies that inhibit a disintegrin and metallloprotease thrombospondin type 1 repeats (ADAMTS13).
- Or it can be congenital (Upshaw-Shulman syndrome) due to inherited deficiency of ADAMTS13.
- Under normal circumstances endothelial cells produce ultralarge von Willebrand Factor (ULvWF) molecules that are cleaved by ADAMTS13 into their typical length multimers.
- In the setting of ADAMTS13 deficiency the ULvWF persists and induces abnormal platelet consumption and RBC fragmentation and destruction.
- HUS does not have ADAMTS13 deficiency and is instead induced by endothelial damage

# Pathophysiology




- ADAMTS-13 protein: cleaves large vWF multimers.
- ADAMTS-13 deficiency: abnormally large vWF multimers accumulate in plasma, reacting with platelets and inducing their adhesion/aggregation.

à disseminated platelet thrombi

à platelet consumption **(thrombocytopenia)** and microangiopathic hemolytic anemia **(MAHA)**

# Presentation

- Full **"Classic Pentad"** (thrombocytopenia, MAHA, neurologic and renal abnormalities, fever) – described in 1966 before plasma exchange was available, occurs only in ~5% of patients
- Neurological abnormalities – 66%, includes minor sx like confusion (31%), and major sx like stroke/seizure/coma (35%).
- Renal failure - 23 %
- Fever - 23%; high fever (>38.9 C), however, is rare and often suggests alternate infectious etiology.
- GI symptoms (vague pain, n/v/d) – 69%! (presumably from intestinal ischemia).
- Weakness/Fatigue – 63%
- Cough – 9%
- Dyspnea – 29%
- Chest pain – 22%

# Tests to Order/Consider – *get before plasma exchange!!*

- CBC with peripheral blood smear
- LDH, T.bili, haptoglobin, reticulocyte count
- ADAMTS-13 assay (activity/antigen and inhibitor/antibody)
- Coombs
- Creatinine.  PT/INR, aPTT, fibrinogen, D-dimer.  LFTs
- Infectious w/u (blood cx, urine cx, hepatitis panel, HIV, stool studies)
- CT/MRI brain (if neuro involvement)
- CT C/A/P – if concerned for malignancy
- Auto-antibody screen, if clinically applicable (eg. ANA, lupus anticoagulant)
- Pregnancy test

# Plasmic Score

Platelet Count < 30 +1

Hemolysis +1

- Reticulocyte Count > 2.5% OR
- Indirect Bilirubin > 2.0 mg/dL OR
- Haptoglobin Undetectable

No Active Cancer in the last year +1

No history of solid organ or HSC transplant +1

MCV < 90 fl +1

INR < 1.5 +1

Creatinine < 2.0 mg/dL +1

| Score - Probability of ADAMTS13 < 10% | |
|---|---|
| 0-4 | 0-4% |
| 5 | 5-24% |
| 6-7 | 62-82% |

# Treatment - Plasmic Score 5-7

TTP (thrombocytopenia + MAHA without alternate clinical cause)

Start daily **therapeutic plasma exchange (TPE)** with 1-1.5 plasma volume within 4-8 hrs.

If TPE not immediately available: give FFP

Consider **corticosteroids**:
1mg/kg/day prednisone or 1g/day Solumedrol depending on severity. No great EBM behind it, and benefit may be limited to patients with true ADAMTS-13 deficiency.

Continue TPE until Platelet > 150K and LDH near normal for 2 days, but maintain CVL until full remission (30 days after last TPE).

Alternative etiology discovered: stop TPE

If no response or relapse, consider:
- TPE **twice** daily,
- **Corticosteroids**
- **Rituximab**

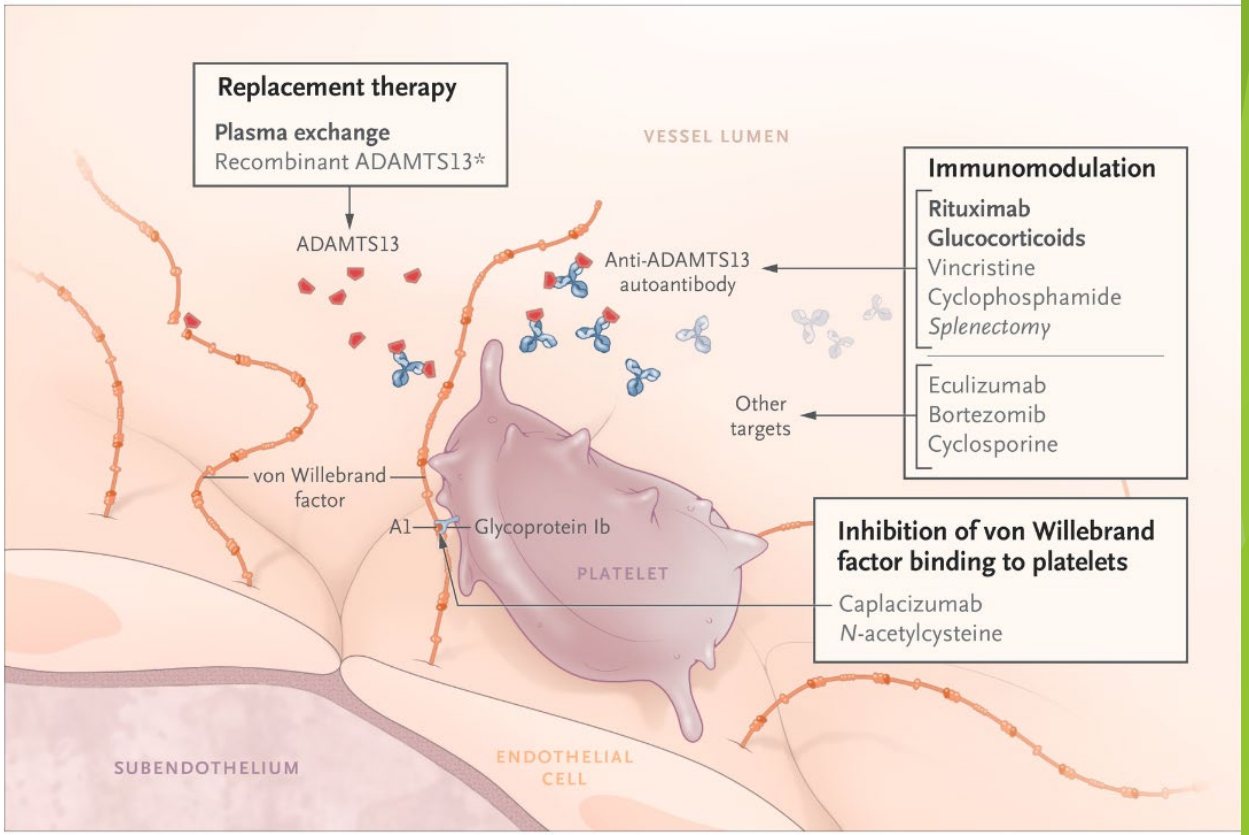
# Diagnostic difficulties and uncertainties

A lot of overlap with HUS. Correct diagnosis does affect treatment.

- TTP – thrombocytopenia + MAHA +/- ADAMTS-13. Could have renal failure. Unclear if cases with normal ADAMTS13 are actually an alternate dx like aHUS.
  - Plasma exchange
- Typical HUS – thrombocytopenia + MAHA + renal failure + diarrhea.
  - Associated with Shiga toxin-producing E.coli (causes endothelial damage then TMA)
  - Only needs supportive care in children; in adults (rare), plasma exchange can be considered if severe neuro sx, otherwise it provides no benefit.
- Atypical HUS – thrombocytopenia + MAHA + renal failure.
- Associated with abnormalities in complement regulation (leading to uncontrolled complement activation à endothelial damage and platelet activation à TMA).
- Both in children and adults. Can be sporadic or familial mutation. Often recurrent.
- Confirm with low C3, genetic testing in patients with severe renal failure, especially if normal ADAMTS13.
- Plasma exchange and eculizumab (anti-C5 antibody) indefinitely.

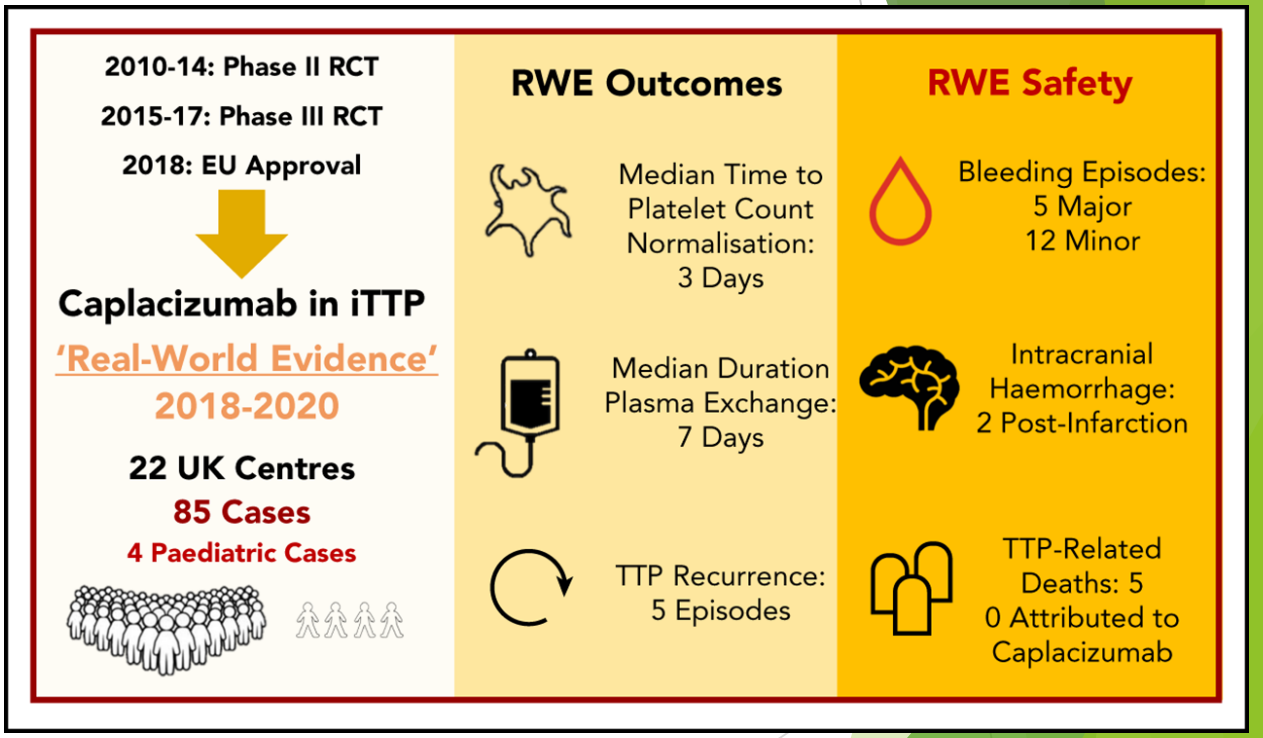
# Caplacizumab

- Caplacizumab, an anti–von Willebrand factor humanized single-variable-domain immunoglobulin (Nanobody), inhibits the interaction between ultralarge von Willebrand factor and platelets.
- Targets the A1 domain of von Willebrand factor (VWF), thereby blocking platelet binding.



# Real-world experience with caplacizumab in the management of acute TTP

Tina Dutt,Rebecca J. Shaw,Matthew Stubbs,Jun Yong,Benjamin Bailiff,Tanya Cranfield,Maeve P. Crowley,Michael Desborough,Toby A. Eyre,Richard Gooding,John Grainger,John Hanley,Joanna Haughton,Joannes Hermans,Quentin Hill,Louise Humphrey,Gillian Lowe,Hamish Lyall,Muhammad Mohsin,Phillip L. R. Nicolson,Nicole Priddee,Alexandros Rampotas,Rachel Rayment,Susan Rhodes,Alice Taylor,William Thomas,Oliver Tomkins,Joost J. Van Veen,Steven Lane,Cheng-Hock Toh,Marie Scully, Real-world experience with caplacizumab in the management of acute TTP, Blood, 2021,



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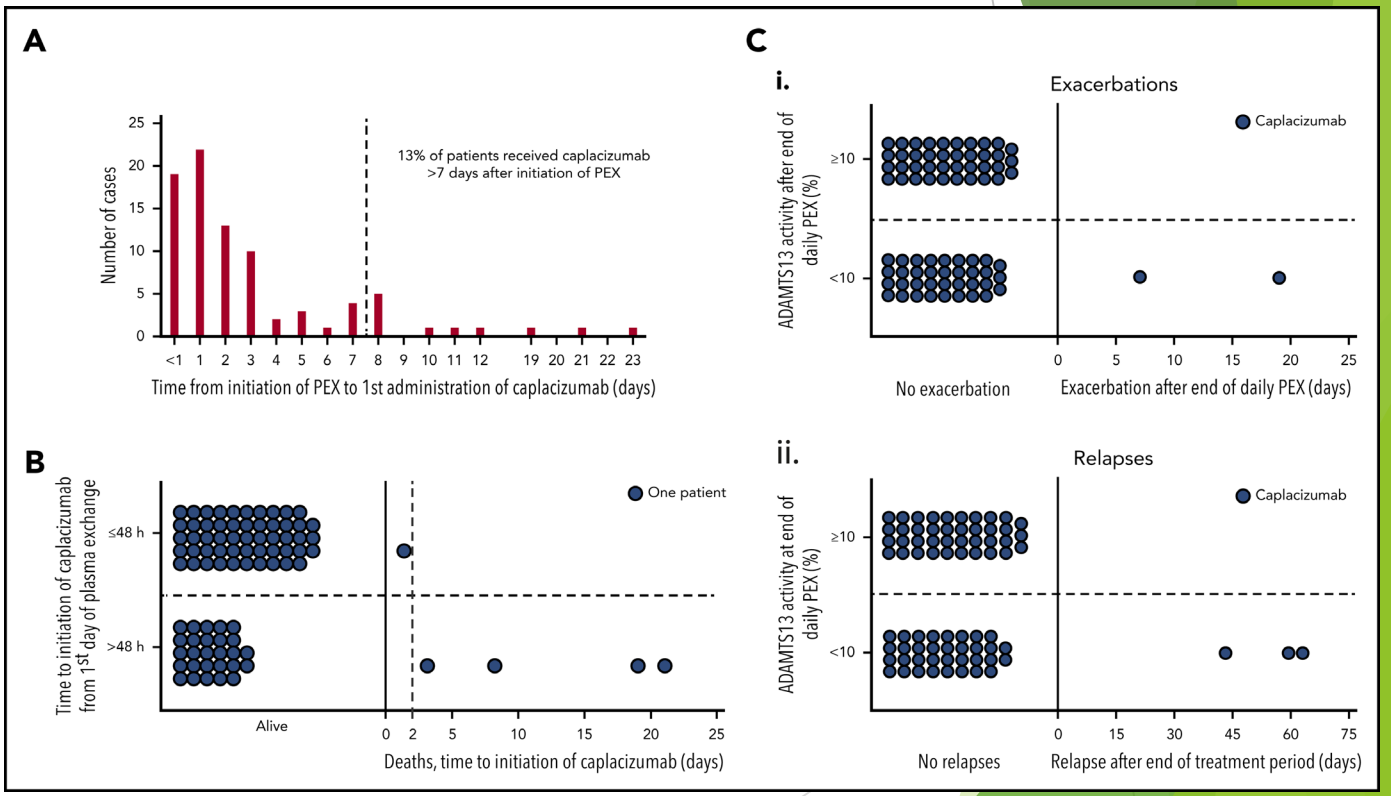
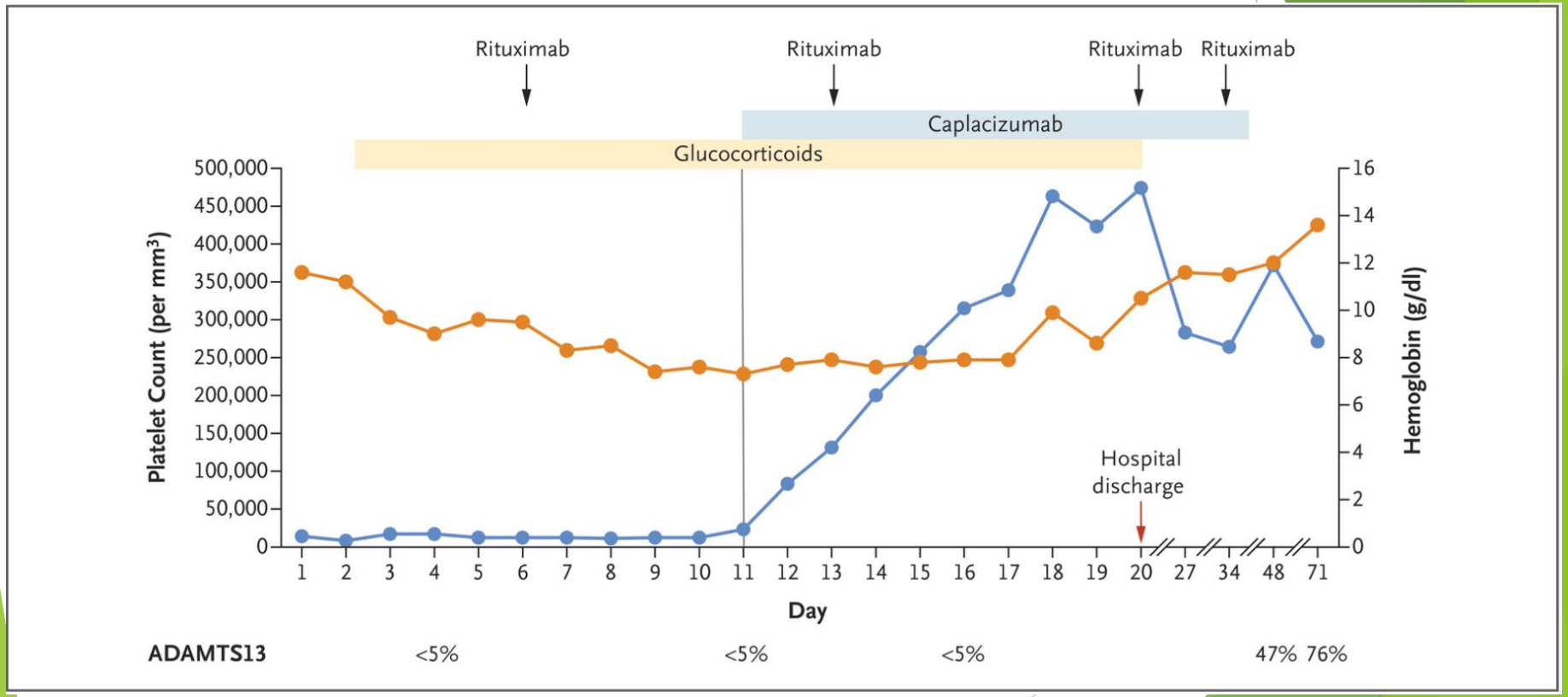


# Case 4 cont… Caplacizumab without PLEX

- Therapeutic plasma exchange has been the essential treatment for acquired thrombotic thrombocytopenic purpura (TTP) since 1991.[1]
- Therefore, the diagnosis of TTP in a Jehovah's Witness patient creates a critical dilemma, because the doctrine of the denomination states that refusal of blood-component transfusion is mandatory. factor multimers and platelets.

- Day 4 and continuing intermittently through day 10, the patient had multiple episodes of transient right facial droop and aphasia.
- She became progressively more confused. On day 7, requested permission to administer caplacizumab.
- On day 11, after regulatory approvals, caplacizumab was initiated at a dose of 10 mg per day, administered intravenously on the first day and then subcutaneously on subsequent days.
- On day 12, the platelet count had increased from 23,000 to 83,000 per microliter; after the third daily treatment, the platelet count had increased to 200,000 per microliter

# Outcome


Rituximab
Rituximab
Rituximab
Rituximab
Caplacizumab
Glucocorticoids
Platelet Count (per mm³)
500,000
450,000
400,000
350,000
300,000
250,000
200,000
150,000
100,000
50,000
0
Hemoglobin (g/dl)
16
14
12
10
8
6
4
2
0
Hospital discharge
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 27 34 48 71
Day
ADAMTS13
<5%
<5%
<5%
47%
76%

# Summary

Oncologic Emergencies Include.

- Acute Leukemia/Burkitt Lymphoma
- SVC Syndrome/Spinal Cord Compression
- Tumor Lysis Syndrome
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- Neutropenic Fever
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- Please call anytime.