Hematologic Complications in the Cancer Patient:
Abnormalities in Hemostasis

Lourdes Rivera, PhD, MCMSc, PA-C
Supervisor, Inpatient APP Consultative Service
Miami Cancer Institute, Baptist Health South Florida
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BAPTIST HEALTH SOUTH FLORIDA

Hematologic Complications in the Cancer Patient

Cytopenias

Anemia-Neutropenia-Thrombocytopenia

- Cancer related
- Hematologic Malignancy
- Myelodysplasia
- Chemotherapy related
- Immune mediated
- Drug Induced/Non chemo
- Aplasia
- Bone marrow failure
- Bone Marrow Infiltration
- Radiation Induced
- HLH

Abnormal Homeostasis

Bleeding and Thrombotic Complications

- Platelet Abnormalities Quantitative
- Platelet Abnormalities Qualitative
- Increase Coagulation factors
- Increase Coagulation Activation Markers
- Coagulopathy/Bleeding
  - Decreased synthesis of anticoagulant proteins
  - Acquired Inhibitors
- Thrombotic manifestations
  - VTE-Arterial/Venous
  - HITT
  - Thrombotic Microangiopathies

References: Carlson, K. and DeSancho, Maria T(2010). Hematological Issues in Critically Ill Patients with Cancer. *Crit Care Clin 26 (2010) 107-132.*

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  - **Thrombotic Microangiopathies**

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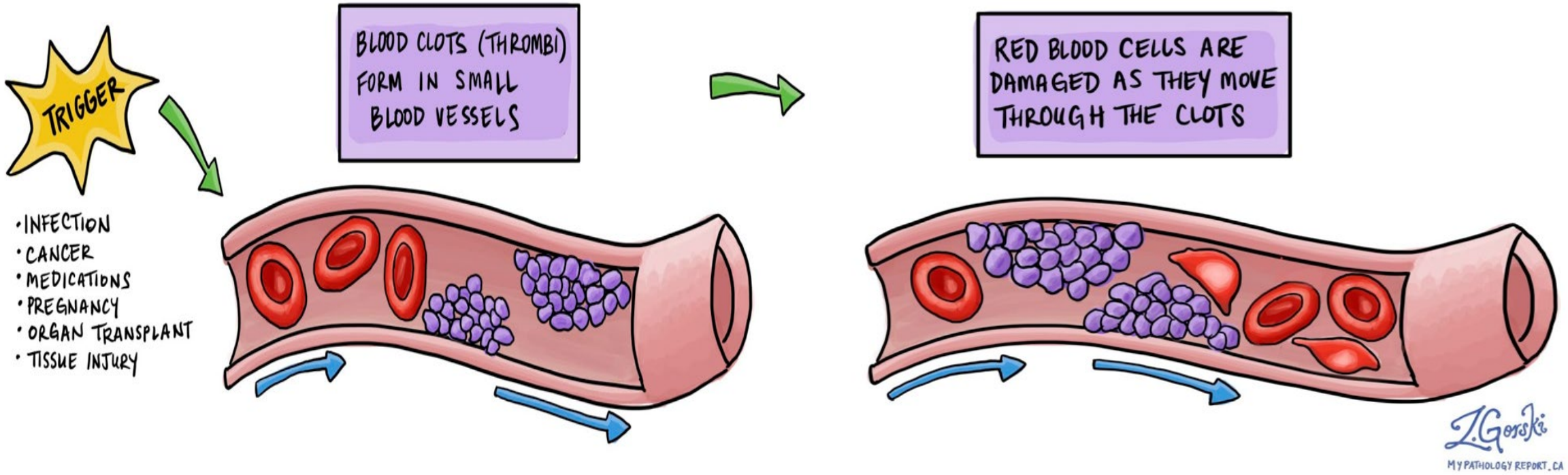
Objectives

- Define and Review Pathophysiology of Thrombotic Microangiopathies (TMAs)
- Describe Laboratory and Clinical Presentation of Primary and Secondary TMAs
- Discuss Clinical Presentation and Management of Cancer Related TMAs
- Compare and Contrast Drug Related TMAs
- Discuss Management of Cancer Related TMAs

Thrombotic Microangiopathy
Definition

Thrombotic Microangiopathy (TMA) is a pathologic term used to describe occlusive microvascular or macrovascular disease with intraluminal thrombus formation defined clinically by microangiopathic hemolytic anemia (MAHA) and thrombocytopenia (MAHAT)



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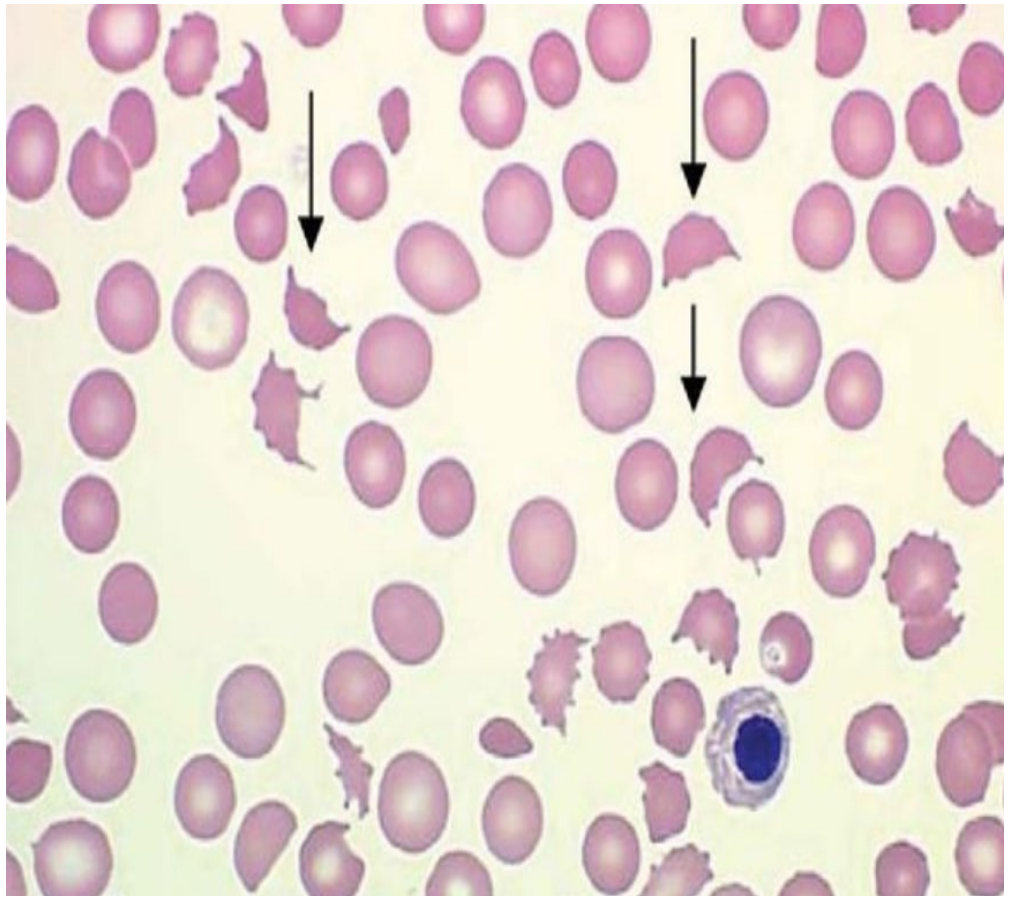
Thrombotic Microangiopathy
Clinical Presentation

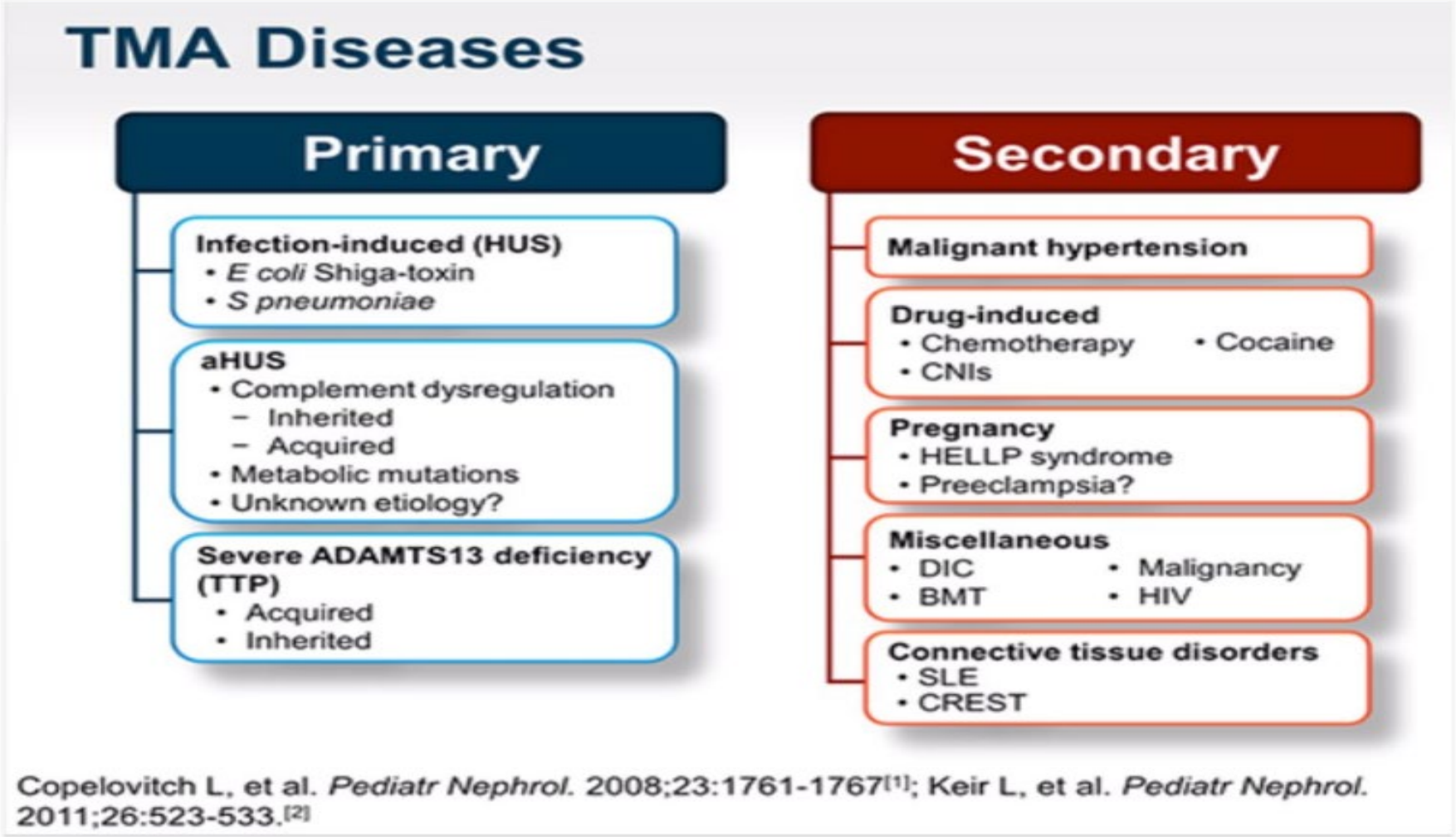
Clinical Presentation

- A **Coombs-negative** MAHA characterized by
  - Elevated serum lactate dehydrogenase (LDH) level
  - Undetectable or markedly decrease serum haptoglobin
  - Presence of schistocytes on a peripheral blood smear
- Thrombocytopenia
- Organ injury: kidney disease, neurologic symptoms and gastrointestinal manifestations, amongst others; kidney involvement may include acute kidney injury (AKI), proteinuria or hypertension (HTN);
- Normal coagulation.



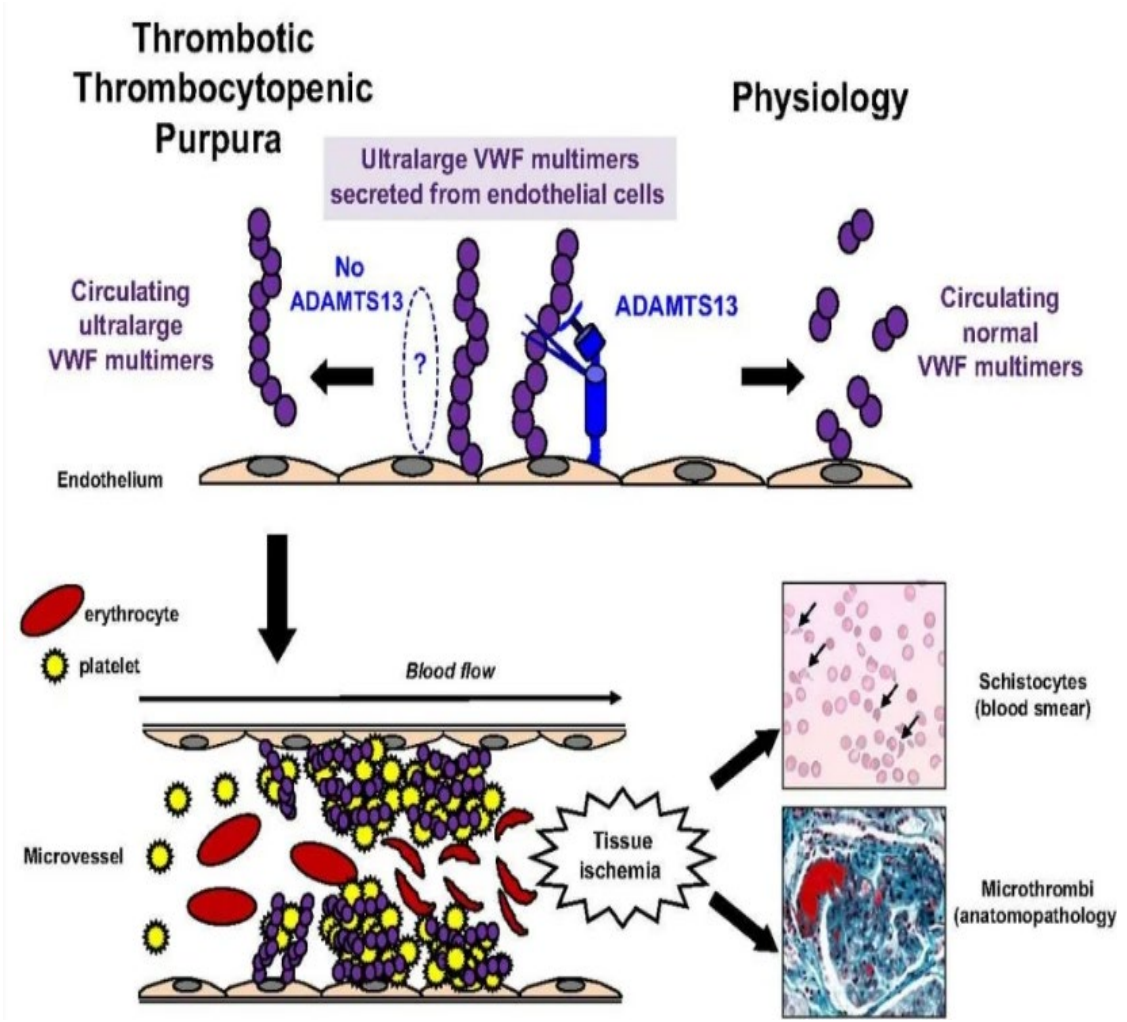
References: Scully et al., Consensus on the standardization of terminology in TTP and related thromb microangiopathies(2017);. 2:Jour Throm Haemo: Vol 15, Iss 2, pp 312-322

Thrombotic Microangiopathy (TMA)

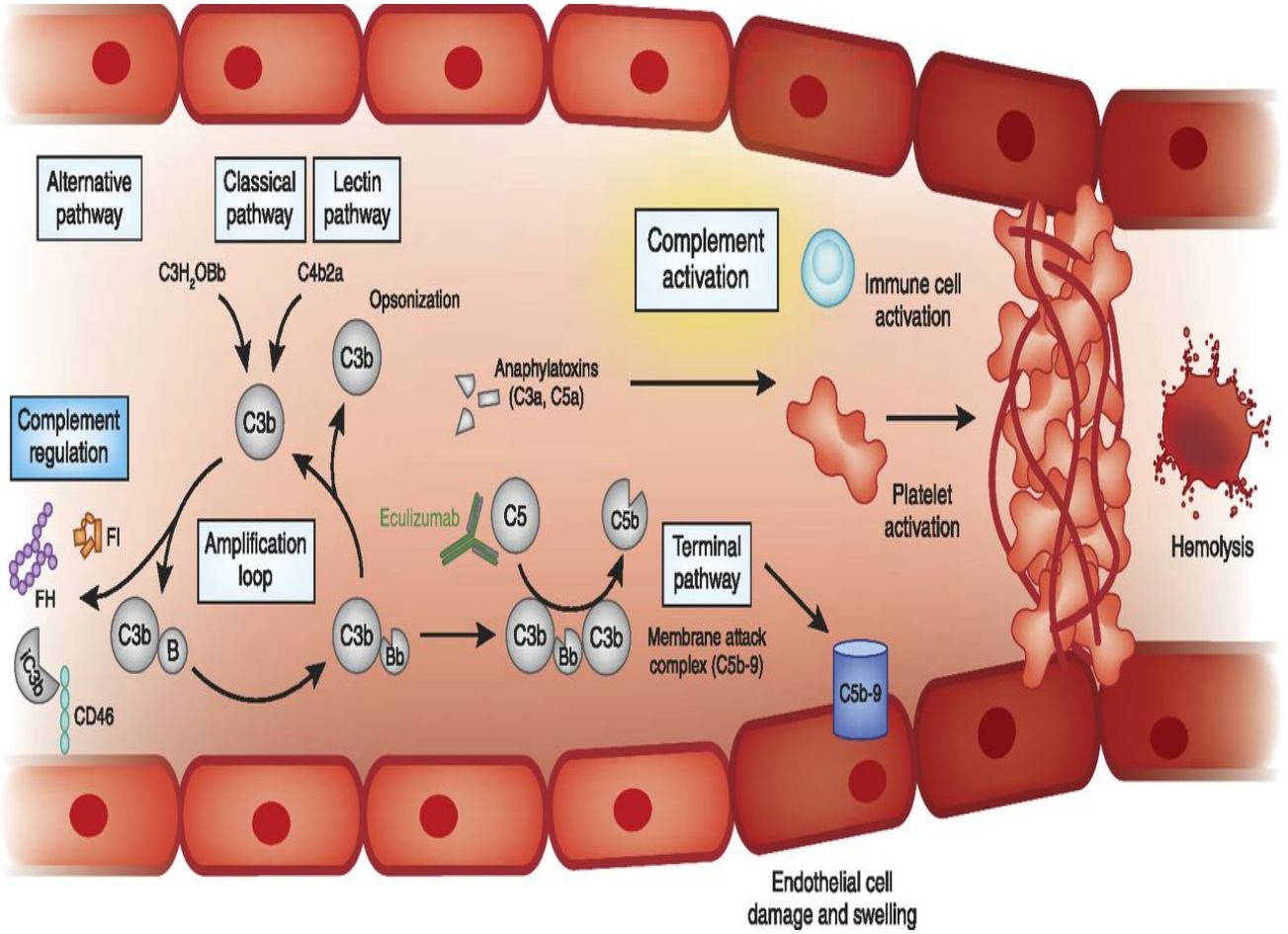


Copelovitch L, et al. *Pediatr Nephrol.* 2008;23:1761-1767[1]; Keir L, et al. *Pediatr Nephrol.* 2011;26:523-533.[2]

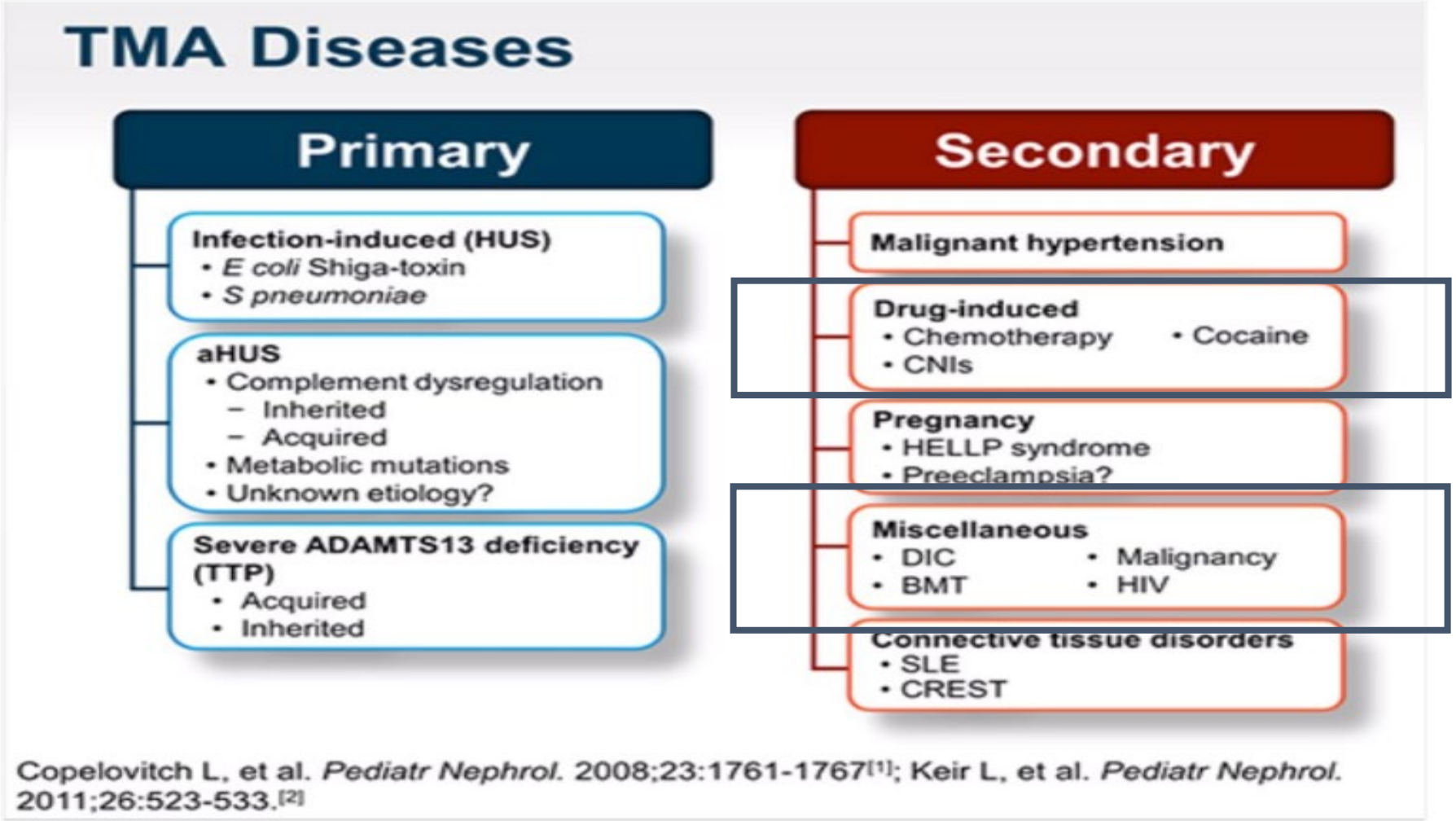
Primary TMA Pathogenesis



Complement Mediated TMA (aHUS)



Thrombotic Microangiopathy
Cancer and Cancer Treatment Related



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Thrombotic Microangiopathy
Case Report

A 52 yo female presenting with progressive dyspnea and weakness for 2 weeks. Brought to the ED with development of abdominal pain and syncope

- Hx of Breast Cancer with LN involvement 3 years prior treated with mastectomy and chemotherapy
- CBC: **Hb 7.5** WBC 5.6, normal differential, **Platelet ct 17K**
- Blood smear: many **schistocytes**
- CT Chest/Abd/Pelvis: WNL
- **LDH 1431**, **haptoglobin <0.1 g/**L, fibrinogen 424 mg/L
- ADAMTS 13: ?

Management

- Clinical diagnosis of TMA was made and urgent Plasmapheresis started, no improvement
- Day 4 developed respiratory distress
- Ct Chest: suggested PE
- Patient died on Day 6
- Autopsy: microvascular clusters of breast cancer cells throughout her lungs and in all organs including bone marrow

Thrombotic Microangiopathy
Cancer Related

Microangiopathic hemolytic anemia and thrombocytopenia in a patient with cancer

- **Cancer-induced TMA**
  - Systemic Microvascular metastases
  - Bone marrow metastases or necrosis
- **Chemotherapy-induced TMA**
  - Dose-dependent antibody reaction
  - Drug-dependent antibody reaction

Presented to: 3nd Annual Advanced Practice Provider (APP) Symposium, December 9-10th, 2022, Virtual
References Published in: Jordan M. Morton; James N. George; *Journal of Oncology Practice* 2016 12523-530.
DOI: 10.1200/JOP.2016.012096

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Thrombotic Microangiopathy
Case Report

A 52 yo male was treated for metastatic cholangiocarcinoma with GEMOX (Gemcitabine plus oxaliplatin regimen) for 6 months followed by gemcitabine maintenance. GEMOX resumed after 4 months with findings of progression of disease.

- Patient presents with hematuria after cycle six. Labs unchanged
- After cycle 7, patient develops fever, chills, lumbar pain and hematuria
- Labs: Hb 9.4gm/dL, plt ct 54K.
- Labs day before Hb 11.6 and plt ct 116K
- LDH 1370, CrCL elevated

Diagnosis of Drug Induced TMA-Immune Mediated

Thrombotic Microangiopathy
Case Report

A 57 yo female was treated for Anal SCC with local-regional disease, Stg Iib, T3N0M0. Initiated on 5-FU and Mitomycin C plus Daily Radiation. Patient presenting to the ED with worsening fatigue, weakness, dysuria and abdominal pain

- Labs: Hb 9.7, Hct 28.4, WBC 0.2, ANC 0.1, Platelet 63. Hb dropped to 5.5 next day
- Pt 13.7, INR 1.19, PTT 27.8, D Dimer elevated
- Na 135, K 4.6, Cr 5.5, baseline 0.9
- Blood smear : Few schistocytes, ADMTS 13 activity 0.55IU (normal 0.68-1.63IU)
- Patient developed resp failure, ARF
- Pan CT Chest/Abd/Pelv/Brain- nonremarkable

Diagnosis of Drug Induced-Dose Dependent

Drug Induced TMA
Dose Dependent vs Antibody Mediated

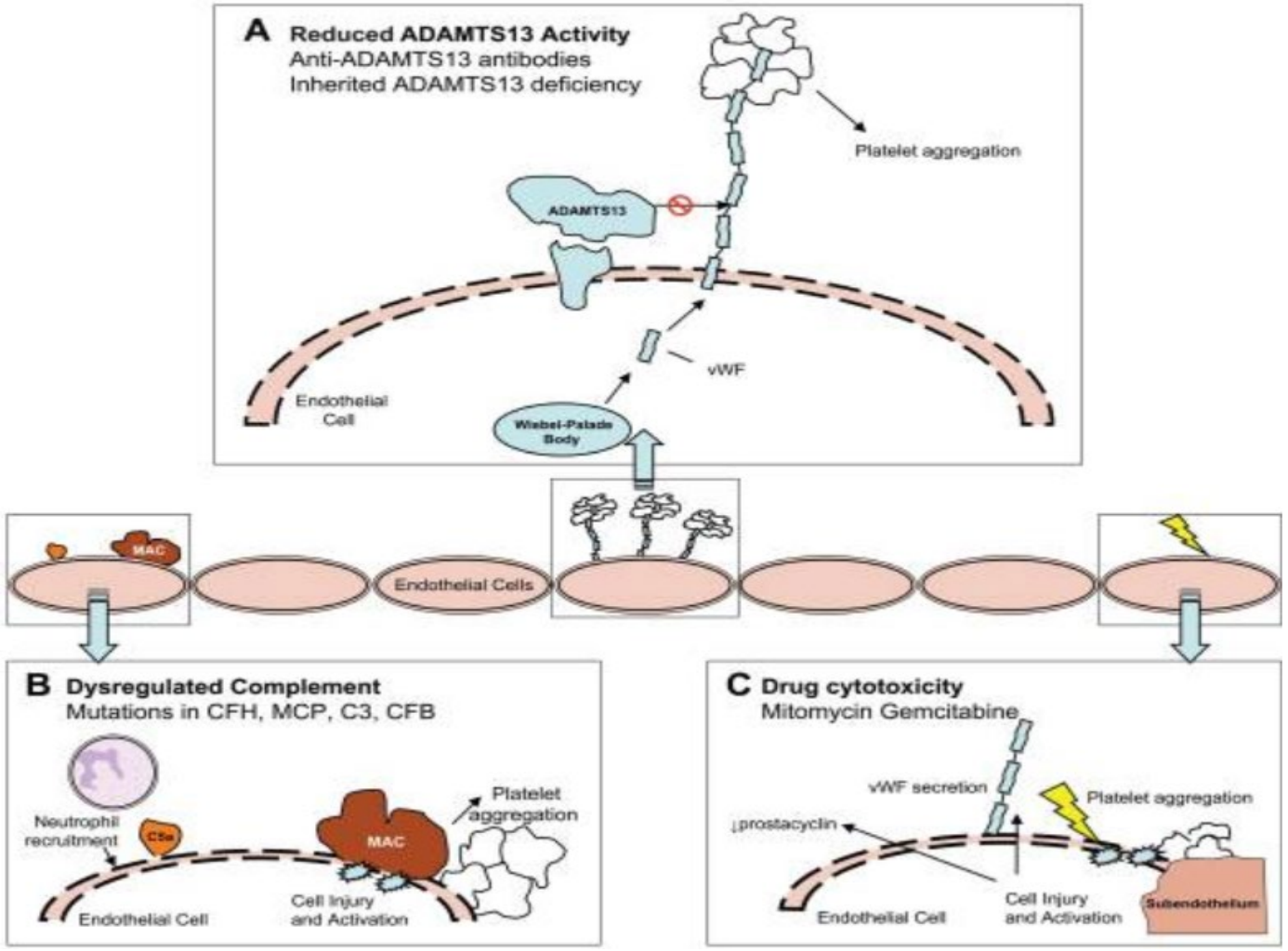
Dose Dependent Drug Induced TMA

- Slowly Progressive Kidney failure
- Accompanying Microangiopathic Hemolytic anemia
- New Onset or Exacerbation HTN months before
- Drugs
  - VEGF Inhibitors
  - Cisplatin
  - Gemcitabine
  - Mitomycin C
  - TKI ? -Sunitinib, Imatinib, Sorafenib
  - PI ?-Bortezomib, Carfilzomib, Ixazomib
- Treatment
  - Immediate and Permanent drug cessation
  - Response to plasmapheresis is poor
  - Few case reports of use of eculizumab with success
  - Prognosis poor with high mortality
  - Persistent Kidney disfunction in recovered patients

Drug Dependent Antibody Induced TMA

- Abrupt onset of systems that recur with drug administration
- Drug dependent antibodies react with Platelets and endothelial cells
- Drugs
  - Gemcitabine
  - Oxaliplatin
  - PI ?-Bortezomib, Carfilzomib, Ixazomib
- Treatment
  - Immediate Drug Cessation
  - Reports of use of Rituxan and Eculizumab with success
  - Data shows no better outcomes in patients treated with plasmapheresis

Chemotherapy Induced TMA



Pathogenesis

A. Decrease in ADAMTS 13 Activity due to Anti-ADAMTS 13 Antibody or Inherited Deficiency
   - Uncleaved VW Multimers lead to Platelet aggregation

B. Mutations in complement proteins lead to Unregulated formation of C5a and C5b9 (Membrane attack Complex)
   - Recruitment of neutrophils
   - Endothelial cell injury,
   - Exposure of the subendothelium
   - Results in a prothrombotic state

C. Drug Cytotoxicity-Dose Dependent
   - Direct injury to the endothelium
   - Decreased levels of prostacyclin
   - Secretion of vWF
   - Exposure of the subendothelium leading to thrombus formation.

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Cancer Induced TMA vs TTP

Clinical Feature	Cancer Related TMA	TTP
Demographics	Older/No Sex or Gender Disparities/ No obesity risk	Young/ 77% women/ Obesity Risk Factor
Presenting Symptoms		
Duration	Gradual	Acute
General	Weakness/ Fatigue/Weight Loss	Fatigue/ No Weight Loss/ Nausea/ Vomiting
Bleeding	Uncommon	Common/ Hematuria/ Petechiae
Respiratory	Common	Uncommon
Pain	Common Back and Bone Pain	Uncommon
Laboratory Data		
Anemia	May be Severe	Typically Severe
Thrombocytopenia	May be Severe	Typically Severe
WBC	May be Increased	May be Increased
Blood Smear	Schistocytes common, nucleated RBCs, immature granulocytes	Schistocytes common, nucleated RBCs uncommon immature granulocytes
ADAMTS 13	Normal or Mildly Decreased	Severely Decreased (<10%)

How To Treat Cancer Related MAHA

Cancer Patient with MAHA

Investigations

- CBC/Ret CT/Blood Smear/Haptoglobin/DAT
- U&E/ LFT/LDH/Troponins/C3/C4
- PT, aPTT, fibrinogen/D Dimers
- Hepatitis serologies/ HIV/ STEC serologies/Stool PCR
- AI Screen: ANA/dsDNA/ENA/aPL/ Preg test
- CT Chest/Abd/Pelvis
- Bone Marrow Biopsy
- Drug History

Thrombocytopenia

Initiate PEX until ADAMTS 13 activity known
Unless diagnosis is Clear

TTP
Adm3 Act <10%
PEX
Steroids
Anti-CD20
Caplacizumab

Cancer TMA
Often AdenoCa or Mets
Do Not PEX
Treat Cancer

Drugs
Stop Culprit Drug
Do Not PEX
?eculizumab for gemcitabine

HUS/STEC-HUS
Supportive Management
CM-HUS
Initial PEX
Eculizumab

Other Causes
Infection Viral
Vit B12 Def
Maling HTN
Autoimmune

Post Transplant
Do Not PEX
After immunosupp
Treat Inf & GVHD
Control BP
?eculizumab

References M. R. Thomas,M. Scully, How I treat microangiopathic hemolytic anemia in patients with cancer, Blood, 2021, Figure 1.

Cancer Related Hematology Considerations
Summary & Key Take-Aways

- Thrombotic Microangiopathy is defined as a Non-Immune intravascular hemolysis with associated thrombocytopenia, organ injury and presence of schistocytes on blood smear
- Differentiation of Primary Tas and Secondary TMAs is essential in order to provide the appropriate management
- Cancer Related TMAs can present clinically differently than Primary TMAs such as TPP.
- Cancer Related TMAs can be related to bone marrow involvement and/or intravascular metastatic disease
- Cancer Treatment Related TMA can be Dose Dependent and/or Antibody Mediated
- Management of TMAs is varied and dependent on etiology. Although plasmapheresis can be first steps in treatment algorithm, it has not been fond to be effective for Cancer related TMAs