Common problems in Hematology

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Long case examination

Approach

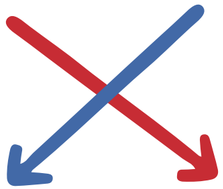
DDx

Investigation

Diagnosis & Management

Hematologic symptoms

Hematologic disease



Organ-specific/systemic symptoms

Non hematologic disease

CBC with blood smear

Imaging

BM examination

SPEP SFLC

Coagulogram

Mixing tests

Common signs & symptoms in hematology

- **Anemia** - fatigue, pallor, dyspnea on exertion
- **Pancytopenia –** Anemia, neutropenia (recurrent infections, fever), thrombocytopenia
- **Bleeding –** ecchymoses, petechiae/purpura, mucosal bleeding, hematoma
- **Thrombosis –** DVT (leg edema), PE (tachycardia, dyspnea), stroke, others
- **Lymphadenopathy –** persistent, firm, non-tender LN
- **Splenomegaly –** early satiety, LUQ fullness
- **Mass –** organ specific symptoms
- **Unexplained fever**

Hematologic diseases

	Common	Rare
Lymphoma	NHL(DLBCL, BL, MZL, CLL, FL), HL	T-cell lymphoma
Myeloid	AML, MPN (CML, PV, ET, PMF)	MDS/MPN (CMML)
Plasma cell disorder	MM, amyloidosis	POEMS, MGCS
Hemolytic anemia	Thalassemia, G-6PD deficiency, AIHA	HS, SAO, PNH
Anemia	Nutritional deficiency anemia, MDS	PRCA
Bleeding	ITP, TTP, hemophilia	Acquired hemophilia, HHT
Thrombosis	APS, CAT	Other thrombophilia
Other		Langerhans cell histiocytosis IgG-4 related disease, Eosinophilia

Clinical approach to anemia

Acute

(< 1 week)

- Acute blood loss
- Acute hemolysis
  - G-6PD with acute hemolysis
  - HbH with acute hemolysis
  - AIHA
  - DIC, TTP/HUS
  - Drug or toxin
  - Infection induced
- Dilutional anemia

Subacute

(weeks to months)

- Pure red cell aplasia
- Acute leukemia
- Myelopthisis
- Aplastic anemia

Chronic anemia

(> 3 months)

- **Chronic hemolysis**
  - Thalassemia, PNH, chronic AIHA
- **Underproduction or ineffective erythropoiesis**
  - MDS
  - Nutritional deficiency
  - Hematologic malignancy
  - Anemia of inflammation
  - Aplastic anemia
  - Myelopthisis
  - Pure red cell aplasia
  - Hormone deficiency

Pancytopenia

Decreased BM production	Peripheral destruction
• Aplastic anemia • BM infiltration : malignancy, myelofibrosis, granulomatous disease, metabolic disorder • Nutritional deficiency: VitB12, folate, copper def • MDS • Drug, toxin, radiotherapy	• Autoimmune • Splenic sequestration • Drug induce immune cytopenia

- PNH
- Connective tissue disease (SLE, RA)
- Hemophagocytic lymphohistiocytosis (HLH)
- Infection (sepsis,HIV,CMV, EBV)
- Malignancy (lymphoma)

Blood Reviews 32 (2018) 361–367

Clinical approach to cytopenia

- **Fever, bleeding** - AA, leukemia, myelopthisis (malignancy, infection)
- **Splenomegaly** – infection, NHL, PMF, autoimmune, ALL, AML M4/5, HLH
- **Massive splenomegaly** – Overt PMF, splenic lymphoma, CML blastic
- **Lymphadenopathy** – lymphoma, Infections, ALL, AML M4/5, metastatic cancer
- **Neurological deficit** – Vitamin B 12 deficiency, paraneoplastic syndrome
- **History of gastric surgery** – Megaloblastic anemia, copper deficiency
- **Jaundice, dark urine** – hemolytic anemia, PNH (pancytopenia, thrombosis)
- **Significant weight loss** – malignancy, chronic infection(disseminated TB)
- **Bone pain** - multiple myeloma, bone metastasis
- **Underlying disease or medication**

Basic investigations for anemia

CBC, PBS (MCV, RDW)

Reticulocyte (CRC, RPI, RI, ARC)

Hemolysis (Reti, LDH, LFT, haptoglobin)

DCT

Low MCV

- Glossitis + RDW > 15 % + thrombocytosis + low reticulocyte count >> IDA
- Hepatosplenomegaly + high RDW + high reticulocyte count >> thalassemia disease
- Normal to mild anemia + RDW high >> thalassemia minor or intermedia

High MCV

- High LDH, high IDB, high reticulocyte, HCT < 3xHb, DAT pos >> cold AIHA
- High LDH, high IDB, low reticulocyte >> ineffective erythropoiesis (B12 def or MDS)

Normal to high MCV

- High LDH, high IDB, high reticulocyte >> hemolysis
- High LDH, high IDB, high reticulocyte, DAT pos >> AIHA
- MCHC > 35 >> hereditary spherocytosis

Iron deficiency anemia

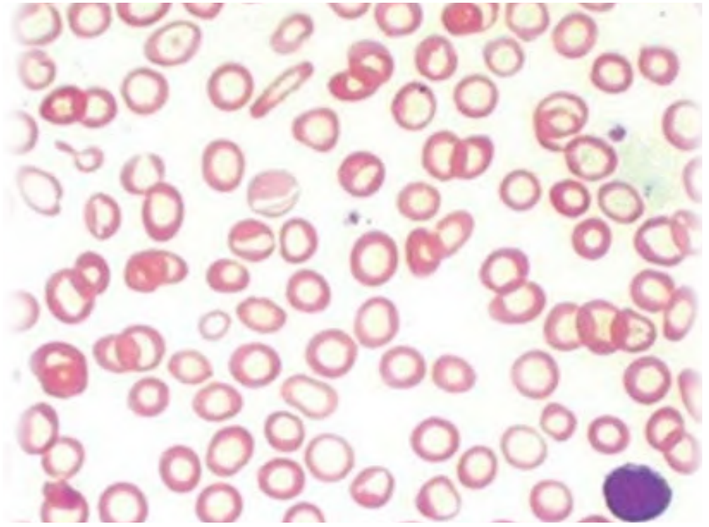
- **S&S** : fatigue, DOE, pica, pagophagia, glossitis, cheilosis, koilonychia
- **Causes** : Gynelogic, GI loss
- **Lab :** HCMC anemia, low ferritin, low TSAT

Plummer-Vinson syndrome

♀ 40-50 years

- Iron-deficiency anemia
- Esophageal webs
  - barium swallowing, videofluoroscopy
- Dysphagia
  - slow-progressing, painless, intermittent
  - usually solid foods

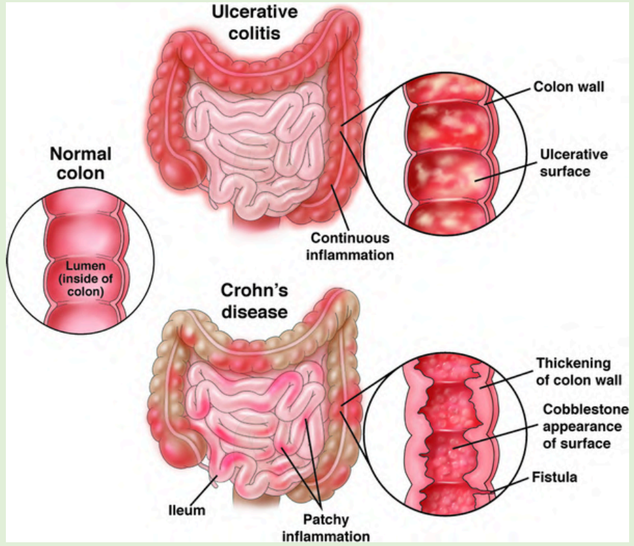
Mx - iron supplement, endoscopic dilatation



Dis Esophagus. 2003;16(2):154-157.

Diseases causing IDA

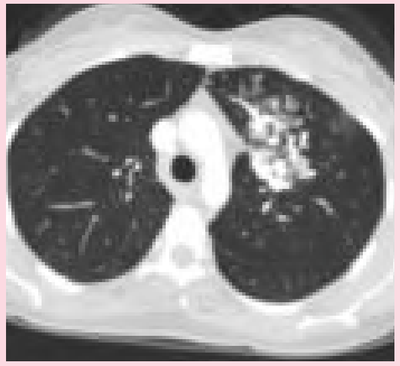
Intest Res. 2014 Oct;12(4):320-7
N Engl J Med 2015;373: e15
J Educ Teach Emerg Med. 2021 Jan 15;6(1):V9-V11
Front. Immunol. 14:1234535



Inflammatory bowel disease

- chronic mucous bloody diarrhea
- abdominal pain, skin lesions
- Lab, stool, endoscopy, patho

Mx : steroid, immunosuppressants



Hereditary hemorrhagic telangiectasia

- Autosomal dominant
- Telangiectasia (skin, mucosa)
- Recurrent epistaxis
- AVM (lung, hepatic, brain, GI)

Definite 3-4
Possible 2/4

Mx : local or systemic, screen AVM(lung, CNS)
iron supplement

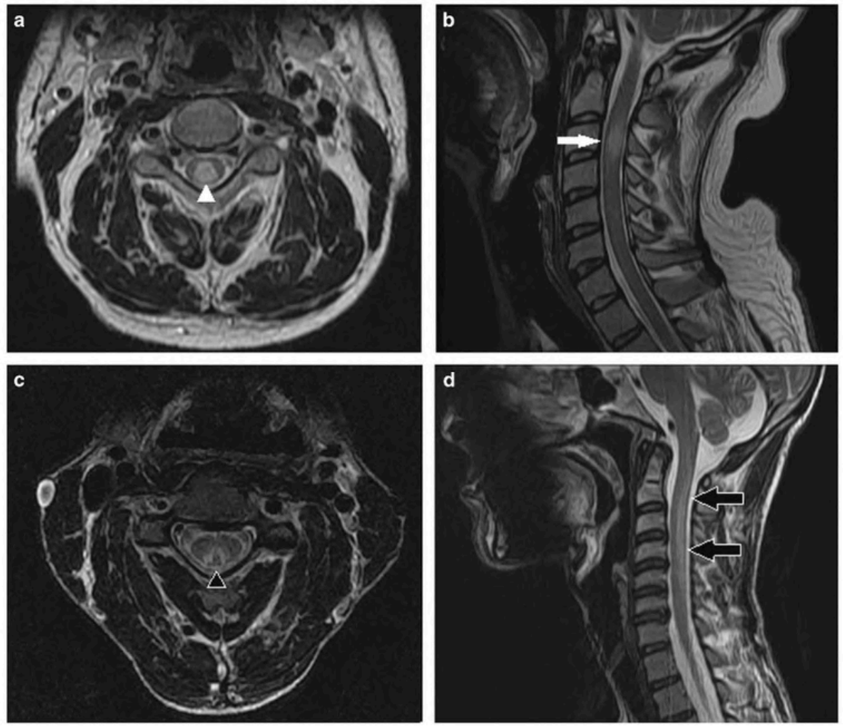
Peutz–Jeghers syndrome (PJS)

- Autosomal dominant
- Mucocutaneous pigmentation
- Harmartomatous polyps in GI tract, GI bleeding , IDA, gut obstruction

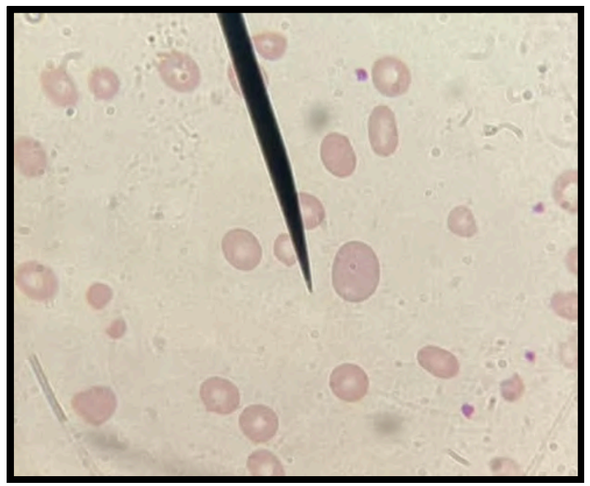
Mx : manage polyps, screen cancer

Megaloblastic anemia

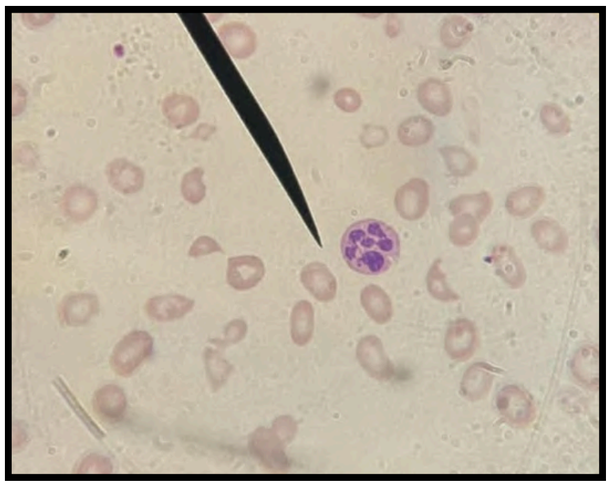
- **S&S** : macrocytic anemia +/- cytopenia, glossitis, angular stomatitis, dementia, hyperpigmentation, progressive tingling and numbness to weakness at hands and feet (Vitamin B12 deficiency)
- **Lab** : PBS (macrocytosis, hypersegmented neutrophils), Low vit B 12, high homocysteine)



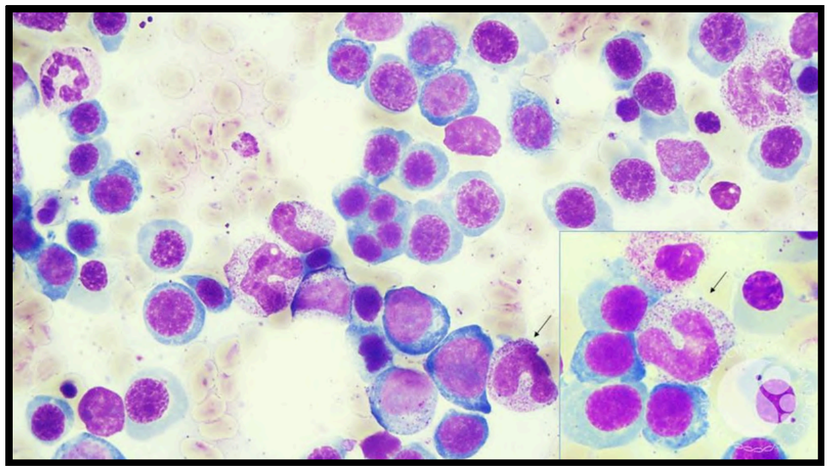
Subacute combined degeneration



Macroovalocyte



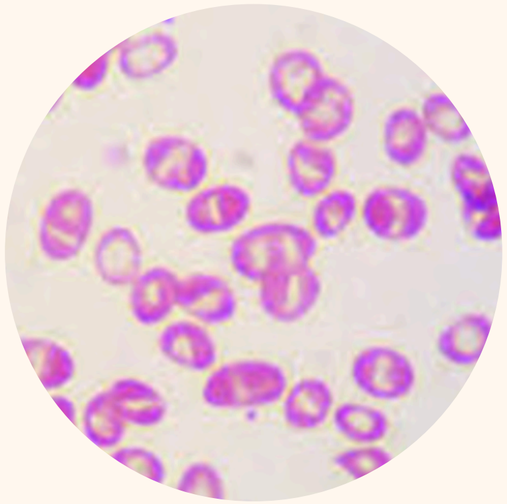
Pseudo-TTP
Hypersegmented neutrophil



Megaloblastic change, giant metamyelocytes

Hereditary hemolytic anemia

- **Hemoglobin abnormalities**
  - Thalassemia, Sickle cell disease
- **Membrane defect**
  - Hereditary spherocytosis
  - Hereditary elliptocytosis
  - Hereditary stomatocytosis
- **Enzyme deficiencies**
  - G6PD, pyruvate kinase deficiency

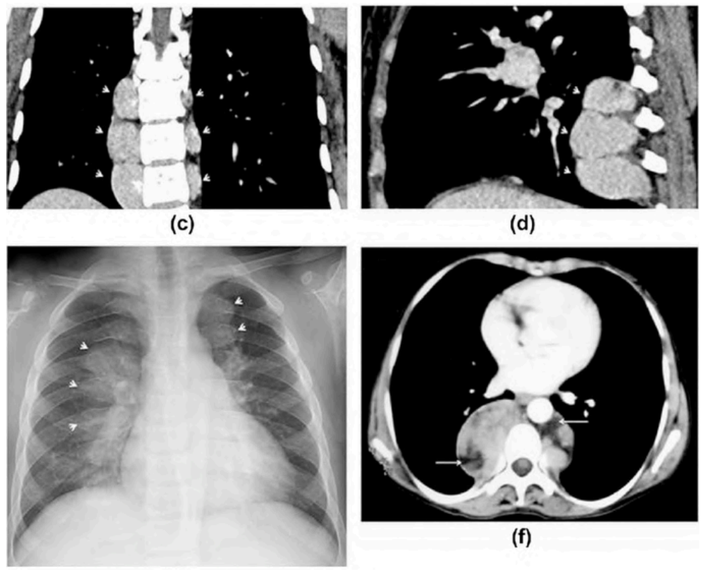


Southeast Asian Ovalocytosis

- extravascular hemolysis: jaundice, mild splenomegaly
- **autosomal dominant**
- associated with **distal RTA: renal stone, nephrocalcinosis**

Thalassemia with complications

Extramedullary hematopoiesis



Gastrointestinal

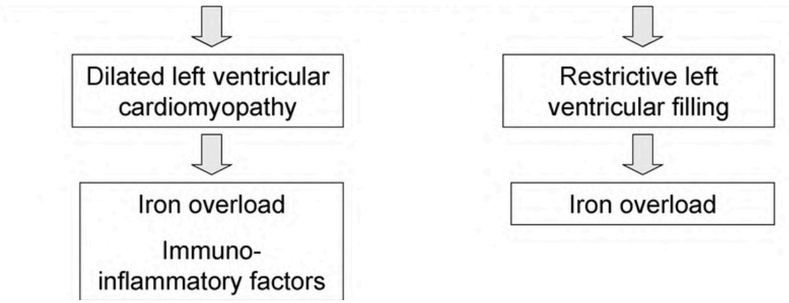
- Hemochromatosis
- Cirrhosis
- Gallstones

Pulmonary hypertension

Endocrine dysfunction

- Diabetes
- Hypothyroidism
- Hypoparathyroidism
- Hypogonadism
- Osteoporosis

Cardiomyopathy



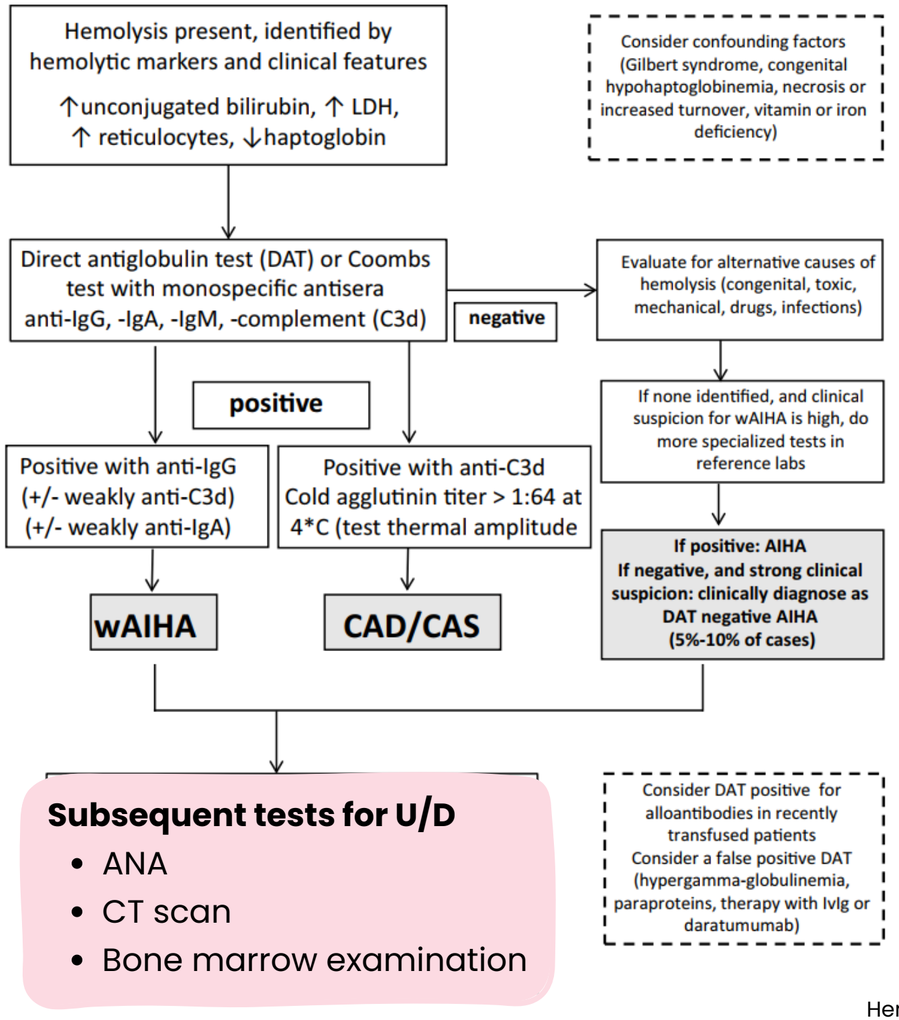
British Dental Journal volume 233, pages931–937 (2022)

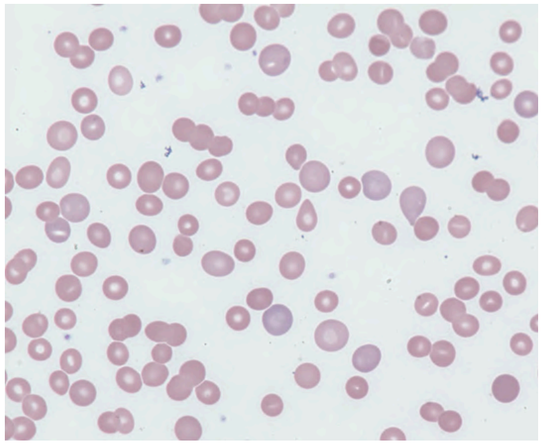
Warm type AIHA

- Warm Ig Ab bind Ag on RBCs at BT 37 C
- Enhanced destruction RBC by macrophages in spleen +/- fixed complement
- Antibody subtype: IgG, Rh
- **Clinical manifestation**
  - Anemia: chronic, acute
  - Hepatosplenomegaly
  - Jaundice

Table 2. Causes of chronic wAIHA

Idiopathic: ~45%
Malignancies: LPDs: ~24%
11% of CLL patients
Even higher after fludarabine treatment
Immune disorders: ~25%
Immune deficiency disorders (common variable immune deficiency)
Autoimmune disorders (systemic lupus, ulcerative colitis)
~10% of patients with systemic lupus
ITP patients (Evans syndrome)
Others: ~5%
Viral infection (usually kids)
Drugs (huge number)



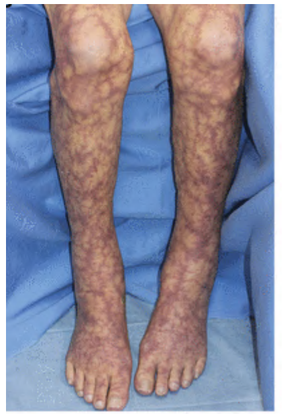


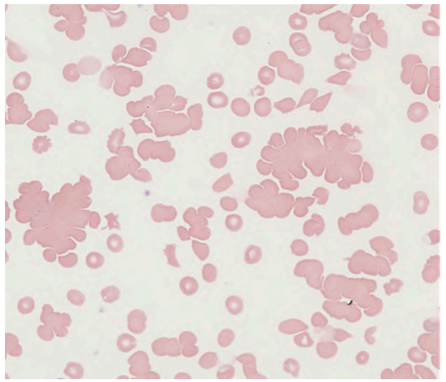
Treatment

- **1st line** - prednisolone 1 mkd for 3 wk then slow tapering and stop in 4-6 mo
- **2nd line** - Rituximab
- **3rd line** - alternative immunosuppressants
- Transfusion if
  - Hb < 6, CVS or neuro instability

Hematology Am Soc Hematol Educ Program. 2025 Dec 5;2025(1):305-311

Cold type AIHA





- Cold Ab bind to Ag on RBCs at BT below 37 C
- Usually IgM class
- Cold agglutinin disease - MGCS
- **Clinical**
  - Extravascular hemolysis +/- intravascular hemolysis (exacerbation)
  - Livedo reticularis, raynaud disease, acrocyanosis and skin necrosis

Primary CAD

- Low grade LPD
- Monoclonal IgM kappa 90%
- Risk of evolution to aggressive lymphoma 3% over 10 years

Secondary CAS

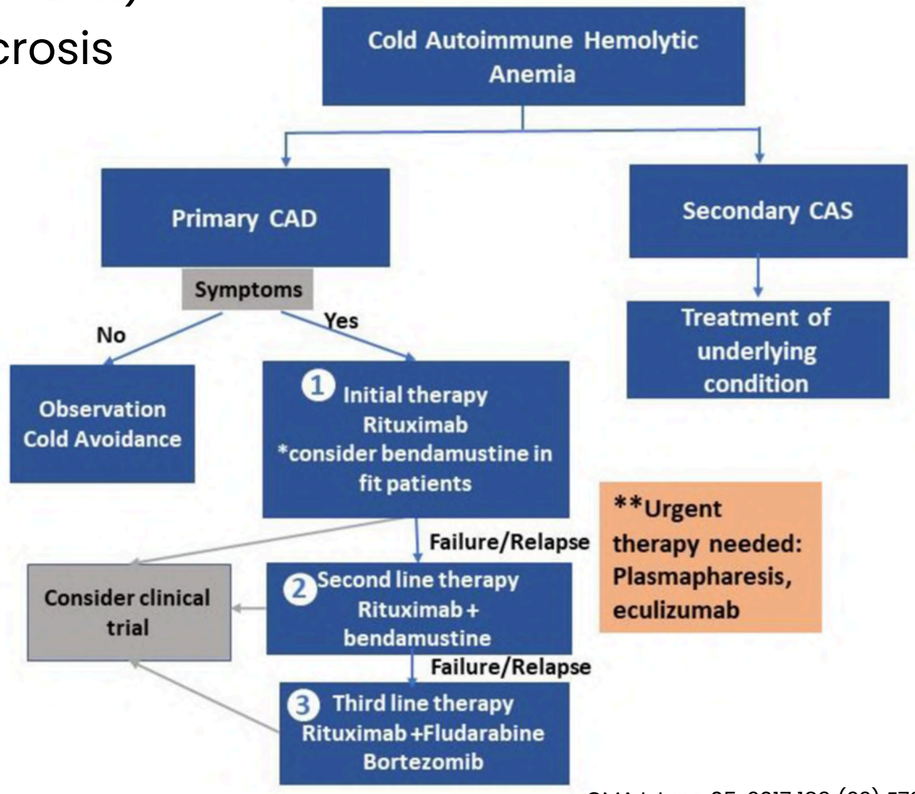
- Infections : M.pneumoniae, EBV, HIV, rubella, flu, Covid19
- Autoimmune : SLE, RA
- Lymphoma (most B-cell) : LPL, NHL

Investigation for diagnosis

- Hemolytic profile
- PBS
- DCT (C3d)
- Cold agglutinin titer > 64 at 4 C

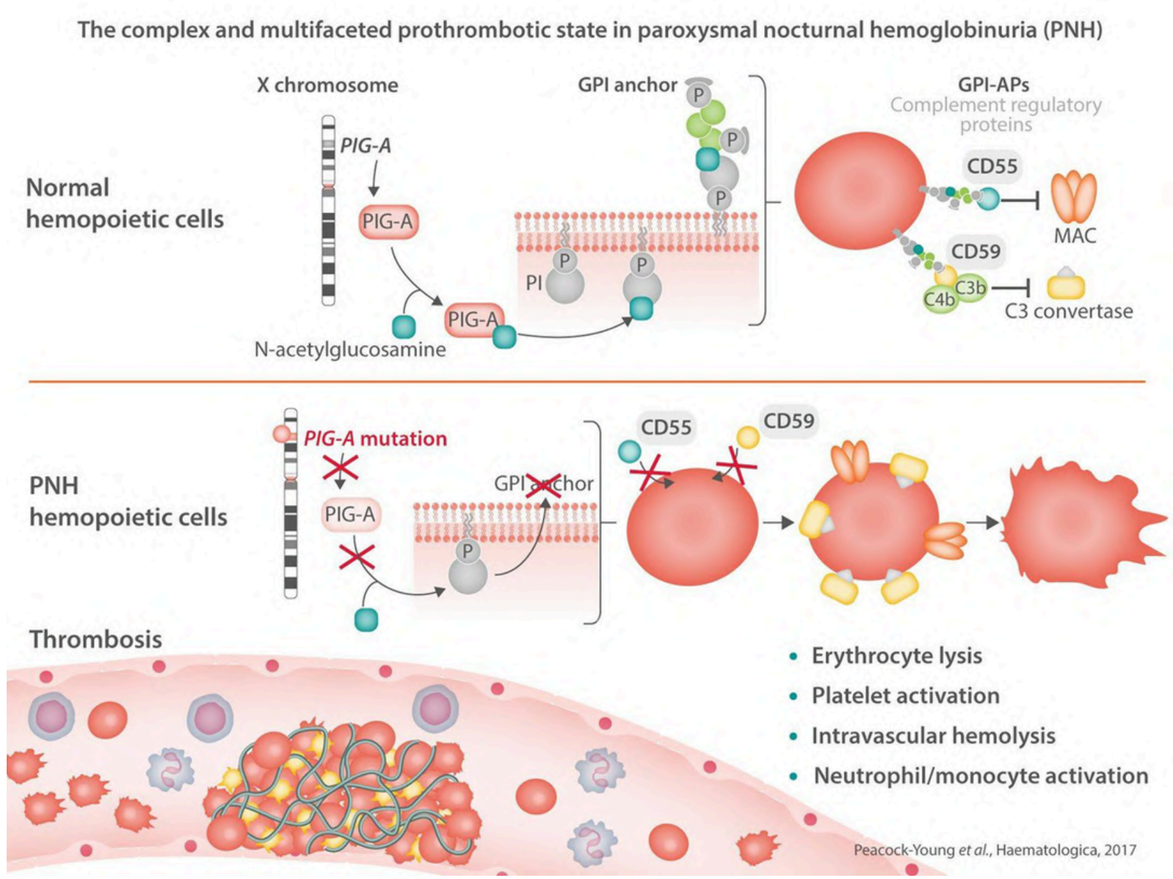
Subsequent tests for U/D

- SPEP, SFLC
- BM study, flow cytometry
- ANA, CT scan
- HIV, HCV, HBV, EBV, mycoplasma



CMAJ June 05, 2017 189 (22) E781
Indian journal of dermatology, venereology and leprology. 80. 575-6.
Hematology Am Soc Hematol Educ Program. 2025 Dec 5;2025(1):295-304.

Paroxysmal nocturnal hemoglobinuria



- Chronic, compliment-mediated intravascular hemolysis
- **Clinical features**
  - **Chronic intravascular hemolytic anemia** +/- IDA
  - **Thrombosis(intraabdominal and cerebral veins)**
  - **Pancytopenia**
  - Smooth muscle contraction, abdominal pain, erectile dysfunction
- **Investigation**
  - Pancytopenia, reticulocytosis
  - Ham's tests
  - **Flow for PNH clone (CD59), FLARE**
- **Treatment**
  - Watch and wait in asymptomatic and mild
  - **Eculizumab**, corticosteroid, androgens
  - Iron supplement, folic supplement, blood transfusion
  - Allo-SCT

Blood (2013) 121 (25): 4985–4996.
Nature Reviews Disease Primers volume 3, Article number: 17028 (2017)

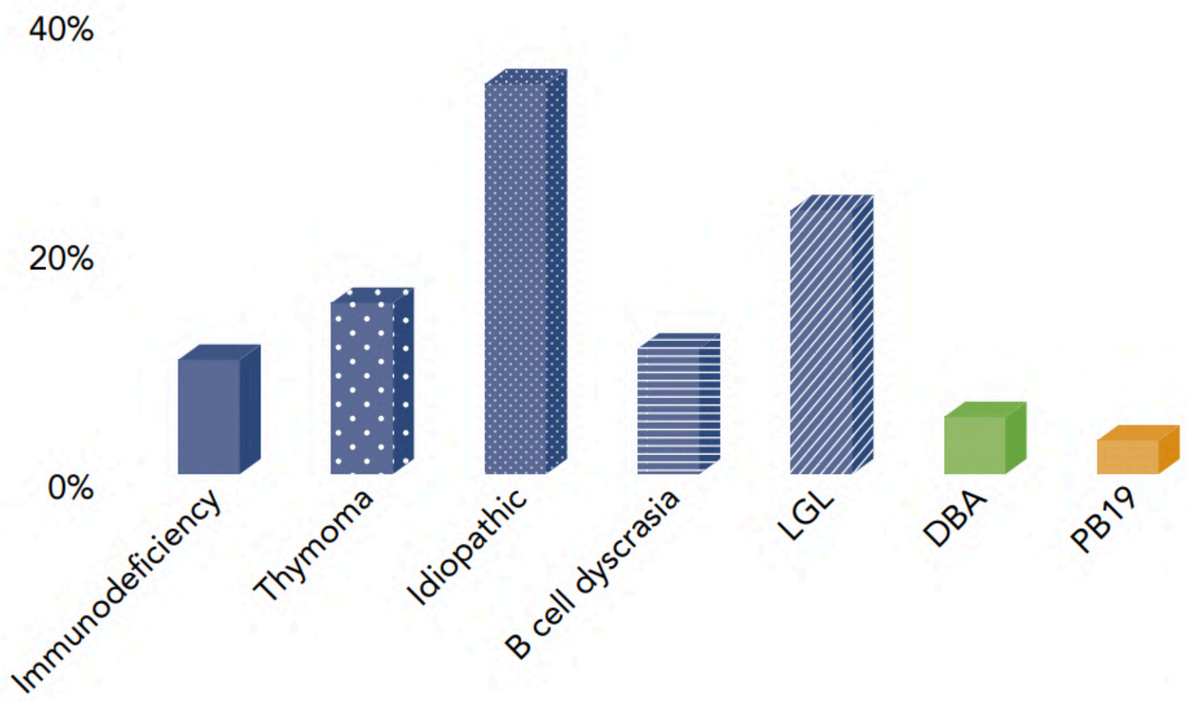
Pure red cell aplasia

Definition

- A syndrome defined by **NCNC anemia** with **severe reticulocytopenia(<1%)** and marked reduction or **absence of erythroid precursors** from BM

Diagnostic criteria

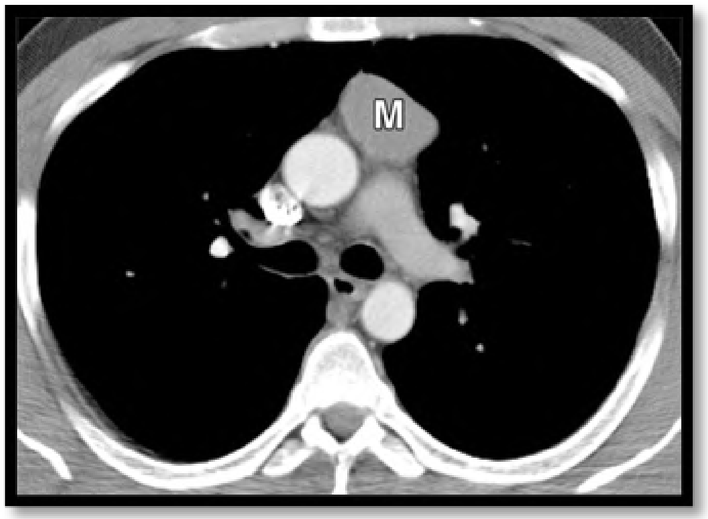
- Fall in RBC 1% per day
- Reticulocyte count <1% or <10,000
- No major change in WBC, platelet
- Normal cellularity of BM with normal myeloid cells and megakaryocytes
- < 1% of erythroblasts (or < 5%)



(Blood. 2021;137(15):2001-2009

Pure red cell aplasia

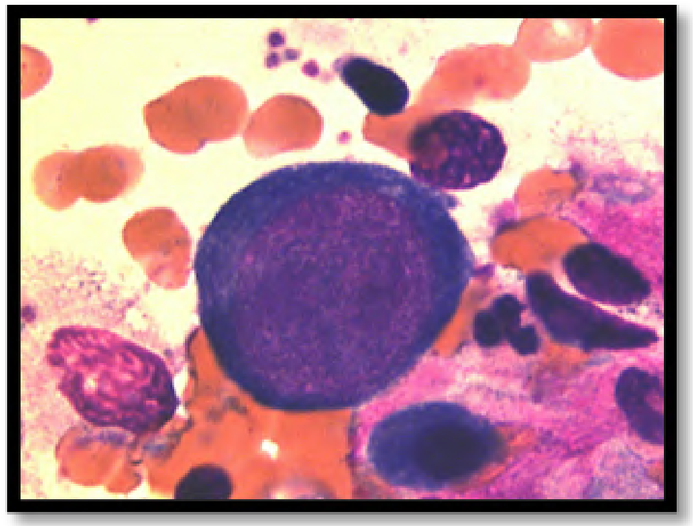
Thymoma



Management

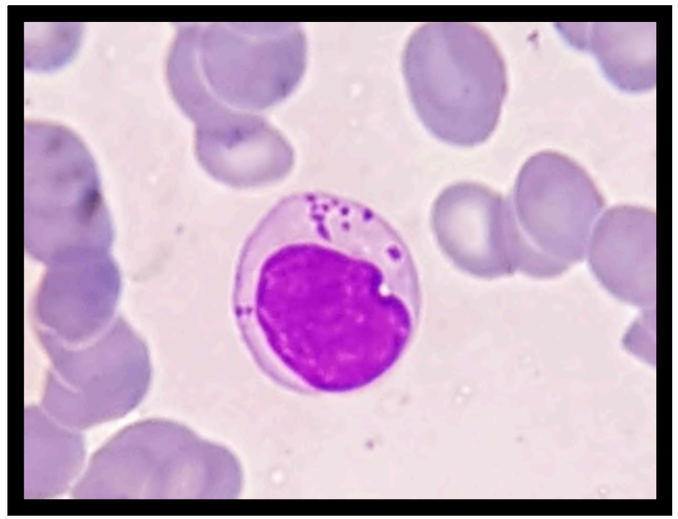
- Thymectomy
- Steroid + IST

Parvo B19



- Immunocompromised patient (HIV, CMT)
- Chronic anemia
- IVIG

LGL leukemia



- Associated with autoimmune disease (RA)
- Neutropenia
- Splenomegaly
- Flow cytometry
- Oral Cy + Prednisolone

Myelophthisic anemia

Definition

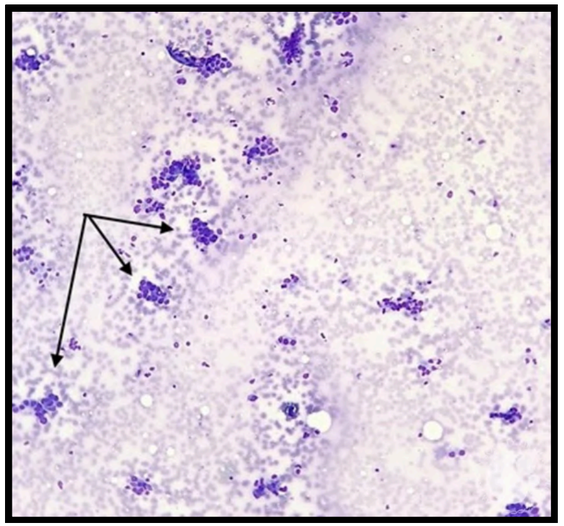
- Anemia resulting from the presence of spotty to massive marrow infiltration with abnormal cells or tissue components

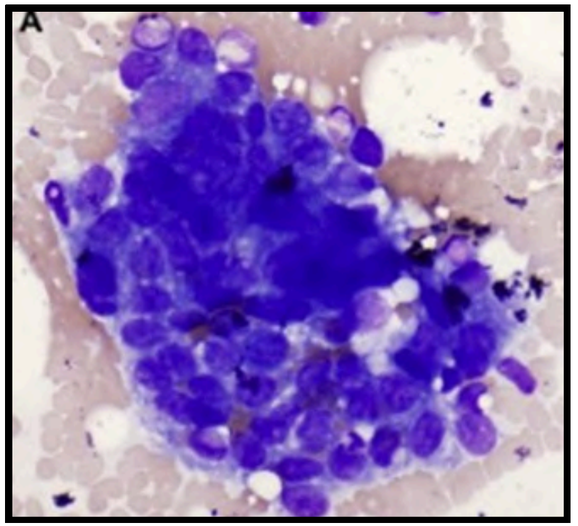
Cause

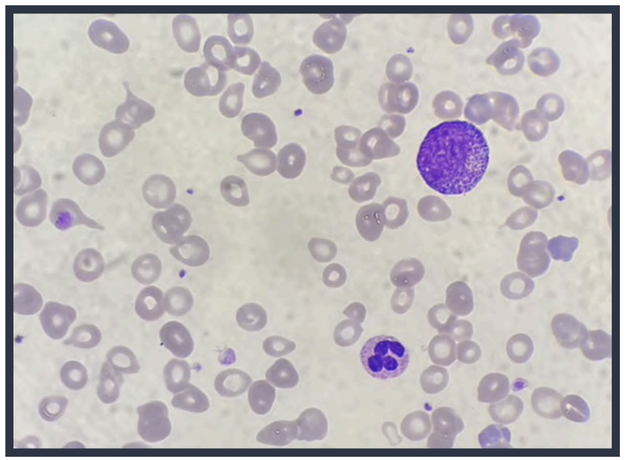
- Metastatic dissemination of the tumor
  - lung, breast, prostate, kidney, and thyroid
- Myelofibrosis
- Granulomatous disease
  - TB, fungus, and sarcoidosis
- Lipid storage disease

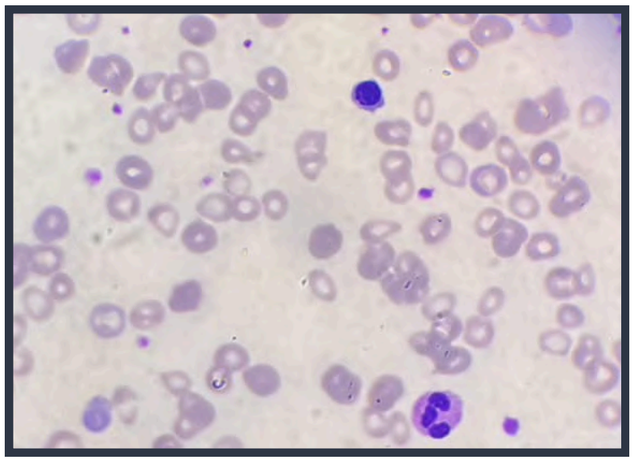
Lab

- Anemia or pancytopenia
- Leukoerythroblastic blood picture



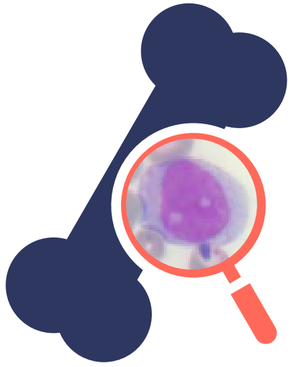






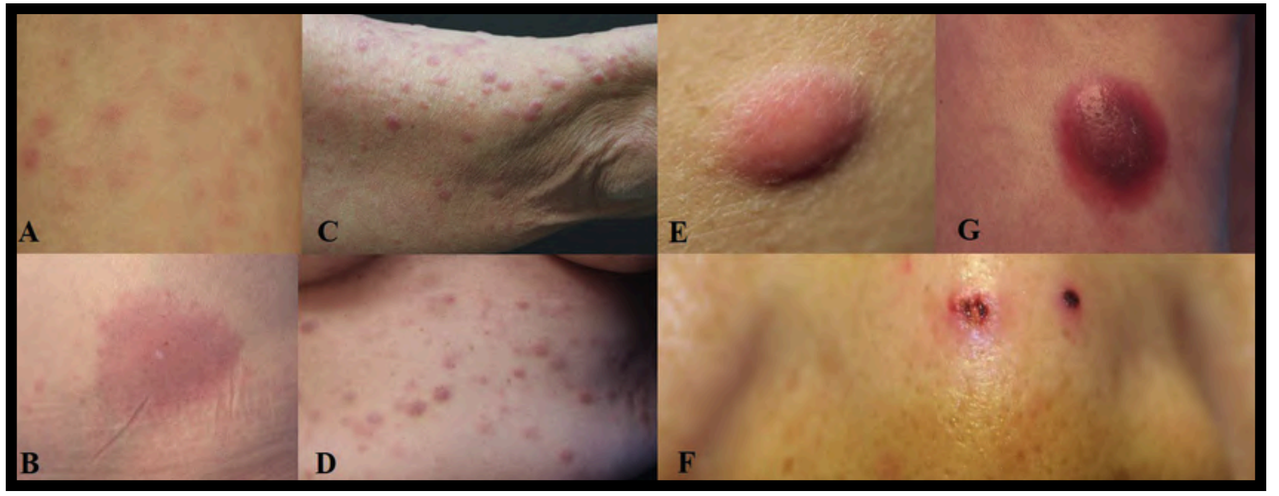
Acute leukemia

Acute to subacute bone marrow failure



Gum hypertrophy (AML M4/5)

Leukemic cutis (AML M4/5)



Acute lymphoblastic leukemia

- Lymphadenopathy, hepatosplenomegaly
- Some, bone pain, oliguria, testicular enlargement, CNS involvement
- Mediastinal mass, SVC syndrome (T-ALL)

Acta Derm Venereol. 2022;102:adv00647.

Approach to bleeding disorder

Local or Systemic → **Primary or Secondary** → **Inherited or Acquired**

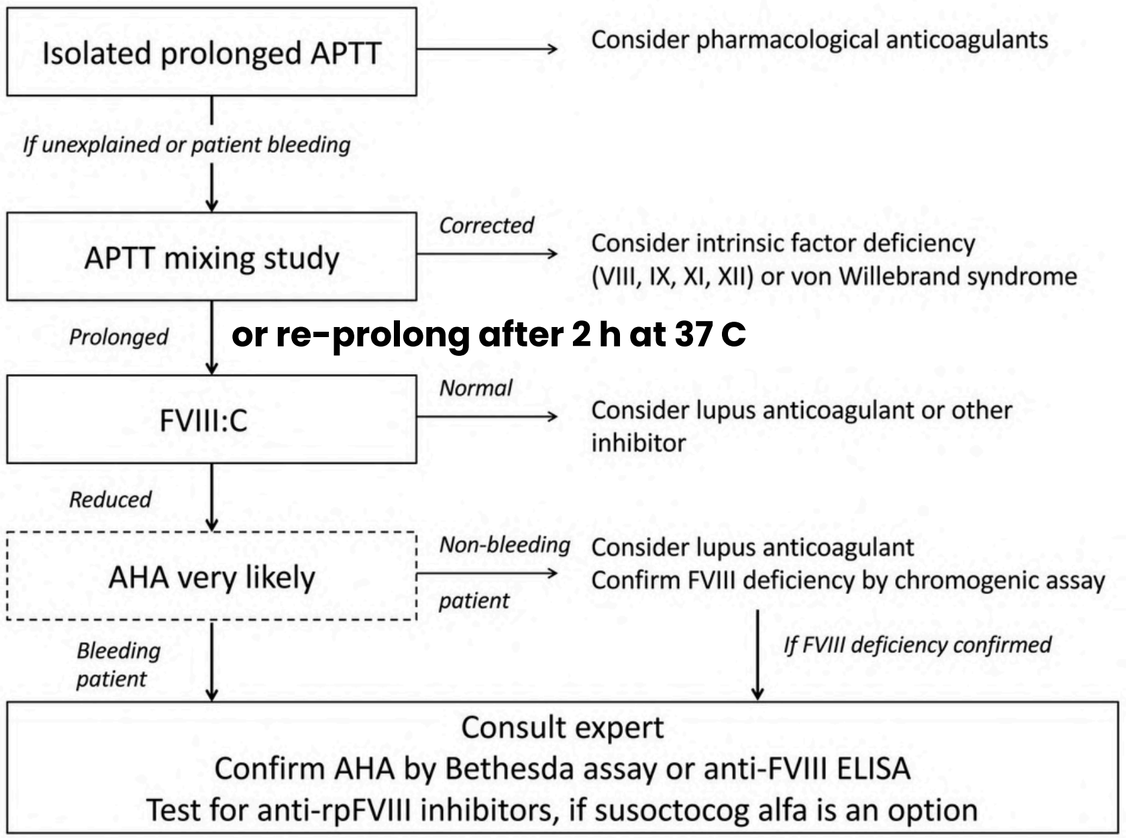
- **Spontaneous bleeding**
- **Multiple site bleeding**
- **Inappropriate bleeding to injury**
- Prolonged bleeding
- Family history of bleeding disorder
- Drug use
- Underlying disease

	Primary	Secondary
Cause	Blood vessel Platelet vWF	Coagulation factor Fibrinolysis Natural anticoagulant
Onset	Immediate	Delay
Site	Superficial ecchymosis Petechiae Mucosal bleeding Menorrhagia	Deep ecchymosis Hematoma Hemarthrosis Intramuscular

- Onset
- History of bleeding
- Family history
- Drug
- Underlying disease

Acquired hemophilia A

- Rare bleeding disorder caused by neutralizing **autoAb against FVIII**
- 50% idiopathic, 50% (autoimmune, malignancy, infection)



Heterogeneous clinical features

- Mucocutaneous bleeding (GI bleed, ecchymosis)
- intramuscular hematoma
- Intracranial hemorrhage
- Postoperative bleeding
- Postpartum hemorrhage

Management

- Control bleeding: **bypassing agent**(rFVIIa, aPCC)
- Eradicate inhibitor: **steroid** +/- cyclophosphamide or RTX

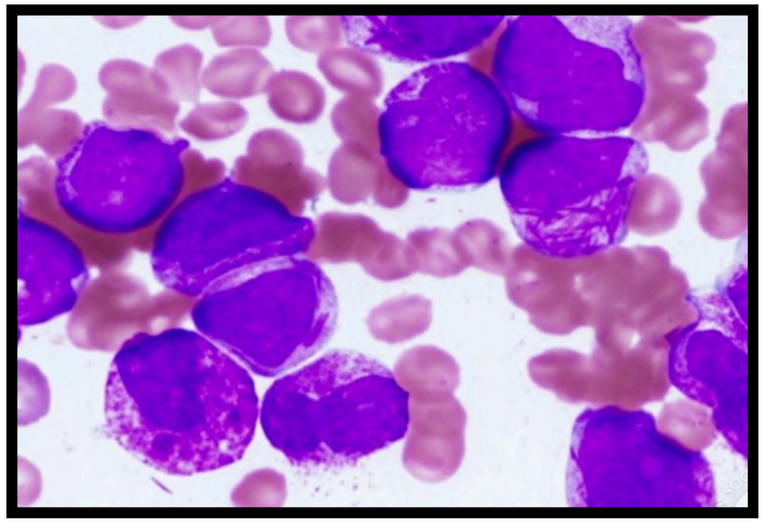
Haematologica. 2020 Jul;105(7):1791-1801.

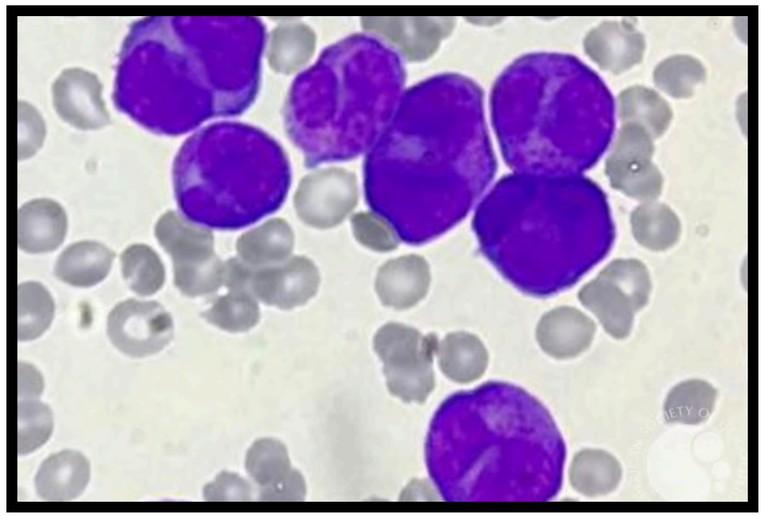
Acute promyelocytic leukemia

Clinical features

- Pancytopenia (most common)
- Severe coagulopathy
  - Disseminated intravascular coagulation (DIC)
  - Primary fibrinolysis
- Thrombosis : DVT, PE

t(15;17)
PML-RARA





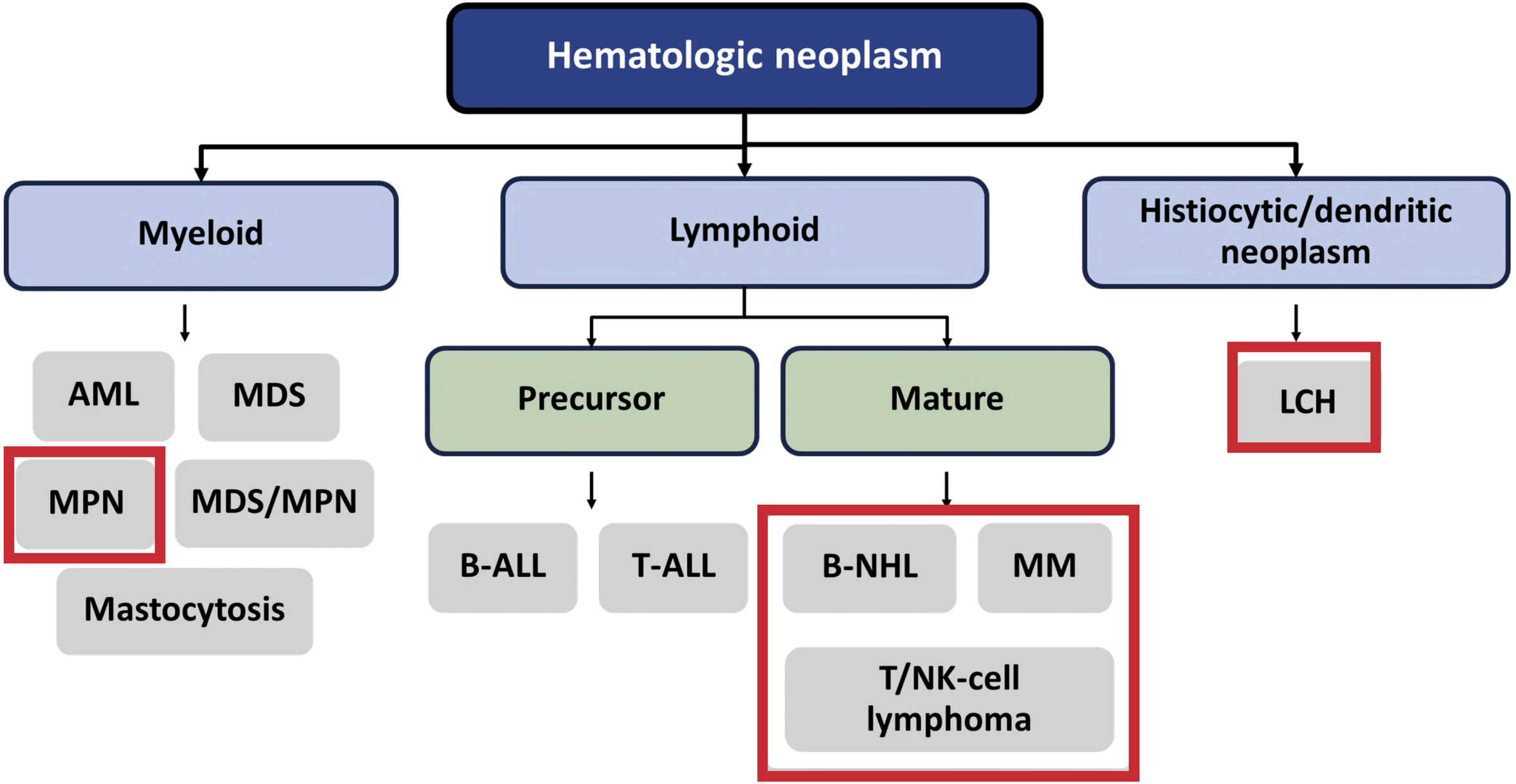
High risk : WBC > 10,000

Intermediate risk : WBC < 10,000 and Platelet < 40,000

Low risk : WBC < 10,000 and Platelet > 40,000

ATRA + ATO (non-HR)

ATRA + Chemotherapy(HR)


Hematologic neoplasm
Myeloid
Lymphoid
Histiocytic/dendritic neoplasm
AML
MDS
MPN
MDS/MPN
Mastocytosis
Precursor
Mature
B-ALL
T-ALL
B-NHL
MM
T/NK-cell lymphoma
LCH

Common manifestations

- **Bone marrow failure**
  - Acute to subacute : AML, ALL, lymphoma with BM involvement
  - Chronic : MDS, MM, PMF, chronic LPD
- **Chronic anemia** : MDS, MM, PMF
- **Constitutional symptoms or B-symptoms**
- **Lymphadenopathy**
  - common disease - lymphoma, ALL, AML M4/5
  - other - RDD, plasmacytoma
- **Splenomegaly** : lymphoma, CML, Ph neg MPN, ALL, AML M4/5
- **Massive splenomegaly** : CML, PMF, splenic lymphoma
- **Thrombosis**
  - Arterial sites : PV, ET
  - Venous sites : lymphoma, leukemia

Other manifestations

- **Fever of unknown origin** : Intravascular lymphoma
- **Extra-nodal** : Skin (T-NHL, IVL), GI (MALT), CNS (NHL), plasmacytoma, histiocytic neoplasm
- **Metabolic disturbances** : Hypercalcemia(MM, lymphoma)
- **Renal failure**: MM, TLS (ALL, BL)
- **Cord compression**: MM, lymphoma
- **Peripheral neuropathy**: POEMS, amyloidosis, LPL
- **Immune phenomenon**: CLL (AIHA, ITP)
- **Vasculitis** : B-NHL (LPL)
- **Endocrine dysfunction** : lymphoma(adrenal), LCH (pituitary)

Case

Case 1 : Generalized Lymphadenopathy

Patient: Male, 35-year-old

Chief Complaint: Enlarged lymph nodes for 6 weeks

Clinical Focus: Lymphadenopathy

Case 3 : Abdominal Mass

Patient: Male, 42-year-old

Chief Complaint: Abdominal discomfort for 1 month.

Clinical Focus: Abdominal Mass

Case 3 : Superior Vena Cava (SVC) Syndrome

Patient: Male, 22-year-old

Chief Complaint: Facial swelling and dyspnea for 2 weeks.

Clinical Focus: SVC Syndrome

- A medical emergency caused by external compression of the SVC.
- Commonly associated with mediastinal masses (e.g., T-cell Lymphoblastic Lymphoma).

Case

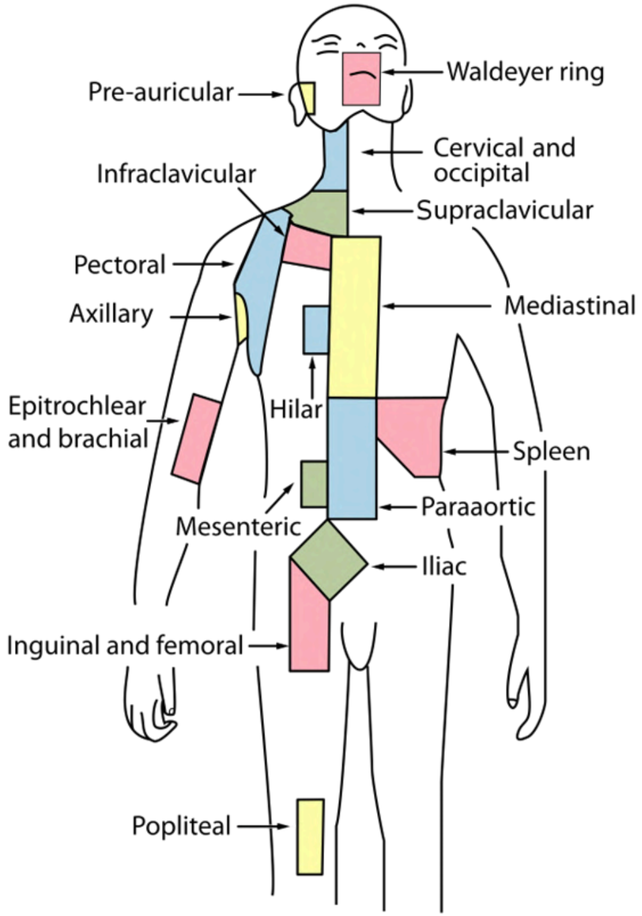
Case 1: Prolonged Fever / FUO
Patient: Female, 72-year-old
Chief Complaint: Prolonged fever for 5 weeks
Clinical focus: FUO

Case 2: Skin Lesion
Patient: Female, 32-year-old
Chief Complaint: Multiple skin rashes for 3 weeks

Case 3: Non variceal bleeding
Patient: Male, 62-year-old
Chief Complaint: UGIB for 3 days with weight loss
Clinical focus: GI lesion

Case 4: CNS Lesion (HIV-Associated)
Patient: Male, 62-year-old with HIV
Chief Complaint: Progressive hemiparesis and memory loss for 8 weeks
Clinical focus: CNS lesion (infection vs malignancy)

Approach to lymphadenopathy



Localized	Generalized
• **Inguinal nodes:** infection of lower limb, STD, abdominal or pelvic malignancy, immunizations • **Axillary nodes:** infections of the upper limb, CA breast, disseminated malignancy, immunizations • **Epitrochlear nodes:** infection of the arm, lymphoma, sarcoidosis • **Left supraclavicular nodes:** metastatic CA from the chest, abdomen (especially stomach—Troisier's sign) or pelvis • **Right supraclavicular nodes:** malignancy from the chest or esophagus • **Cervical nodes:** CA oropharynx and head & neck	• **Infection:** viral, TB, bacterial, NTM, fungus • **Neoplasm:** lymphoma, leukemia, metastatic cancer • **CNT disease:** SLE, RA, DM • **Infiltrative:** sarcoidosis, amyloidosis, Castleman's disease, Kikuchi's • **Drug:** hydralazine, carbamazepine • **Others**

Clinical mimics of lymphoma

- Kikuchi's disease

  acute to subacute, painful, tender, enlarged cervical LN (2-4 cm),
  fever, constitutional symptom, various skin lesion, leukopenia
  self-limited (within 3 month) -> conservative treatment

- Rosai-Dorfman disease

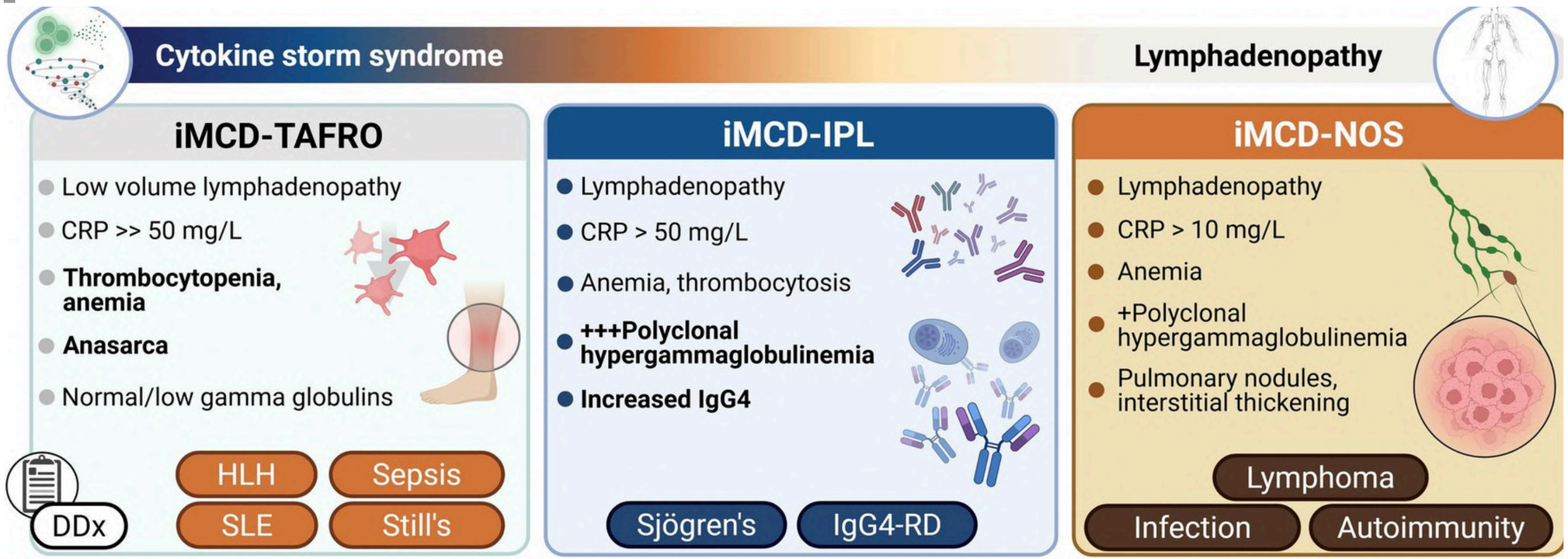
  bilateral, massive, and painless cervical lymphadenopathy
  constitutional symptom, less extranodal (skin, CNS, nasal sinus)
  polyclonal hypergammaglobulinemia, elevated ESR
  isolated RDD or associated with malignancy, autoimmune

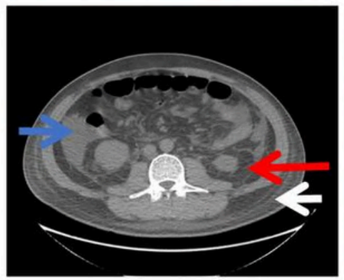
- Castleman's disease

  Unicentric - slow-growing, non-malignant painless solitary mass
  Multicentric - constitutional symptom, splenomegaly, polyclonal hypergammaglobulinemia, fluid accumulation (edema, effusion), high ESR, anemia, thrombocytopenia, renal dysfunction, hypoalbuminemia, lymphocytic interstitial pneumonitis, violaceous papules
  Treatment - UCD(surgery)**,** iMCD (anti-IL6), HHV8-MCD(rituximab,etoposide), POEMS (MM-Rx)

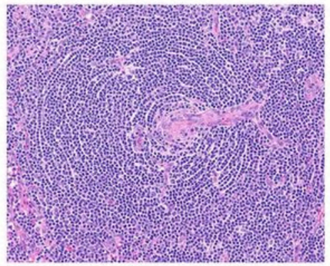
Brown, Jennifer R. and Arthur T. Skarin. "Clinical mimics of lymphoma." The oncologist 9 4 (2004): 406-16

Idiopathic MCD

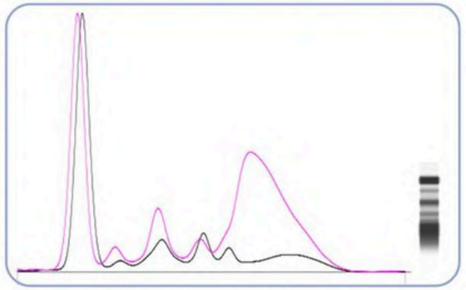




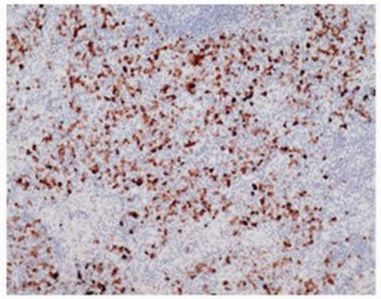
CT images demonstrating ascites (blue arrow), retroperitoneal standing (red arrow) and subcutaneous edema (white arrow) in a patient with TAFRO



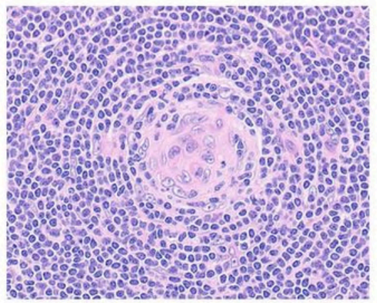
Prominent vascularity. Follicle with a radial vessel reaching the germinal center (the lollipop sign), in a patient with iMCD-TAFRO



Polyclonal hypergammaglobulinemia



Increased IgG4+ plasma cells >100/hpf in a patient with iMCD-IPL and plasma cell histology



Prominent follicular dendritic cells in a patient with iMCD-NOS

Abbreviations: **TAFRO** (thrombocytopenia, anasarca, fever, renal dysfunction/reticulin fibrosis, organomegaly), **IPL** (Idiopathic Plasmacytic Lymphadenopathy), **NOS** (Not Otherwise Specified), CRP (C-reactive protein), IgG4-RD (IgG4-related disease), HLH (hemophagocytic lymphohistiocytosis), SLE (systemic lupus erythematosus)

Chen LYC, Zhang L, Fajgenbaum DC. Expert perspective: diagnosis and treatment of Castleman disease. Arthritis Rheumatol 2025.

Arthritis & Rheumatology ACR American College of Rheumatology

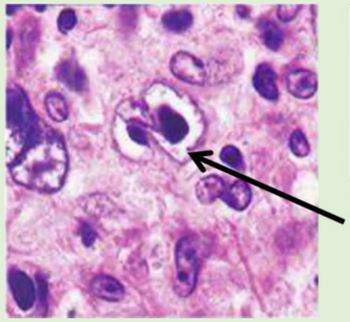
Approach to lymphoma

10 %

90 %

Hodgkin Lymphoma

- Classical HL
- NLPHL



Reed-Sternberg cell

- Bimodal age
- Nodal presentation

Non-Hodgkin Lymphoma

Indolent

- **B-cell**
  - FL
  - SLL/CLL
  - MZL
  - LPL
  - Indolent MCL
- **T/NK-cell**
  - MF/SS
  - LGL
  - Chronic NKL

Aggressive

- **B-cell**
  - DLBCL
  - MCL
- **T/NK-cell**
  - ALCL
  - AITL
  - PTCL NOS
  - ENKTL
  - SPTCL

Highly aggressive

- **B-cell**
  - BL
- **T/NK-cell**
  - ANKL

Clinical manifestations of lymphoma

Common

- Painless lymphadenopathy
- B-symptoms
  - fever, unexplained weight loss, night sweat
- Extranodal manifestation
  - GI, skin, CNS
- Abnormal CBC

Unusual

- Extranodal mass - other sites
- Body cavity fluid
- Lactic acidosis and hypoglycemia
- Immune cytopenia
  - AIHA, CAS, ITP
- Chronic diarrhea
- Peripheral neuropathy
- Cholestasis - infiltrative, VBDS
- Endocrine dysfunction
  - hypercalcemia
- Cerebral infarction

Common manifestations of lymphoma

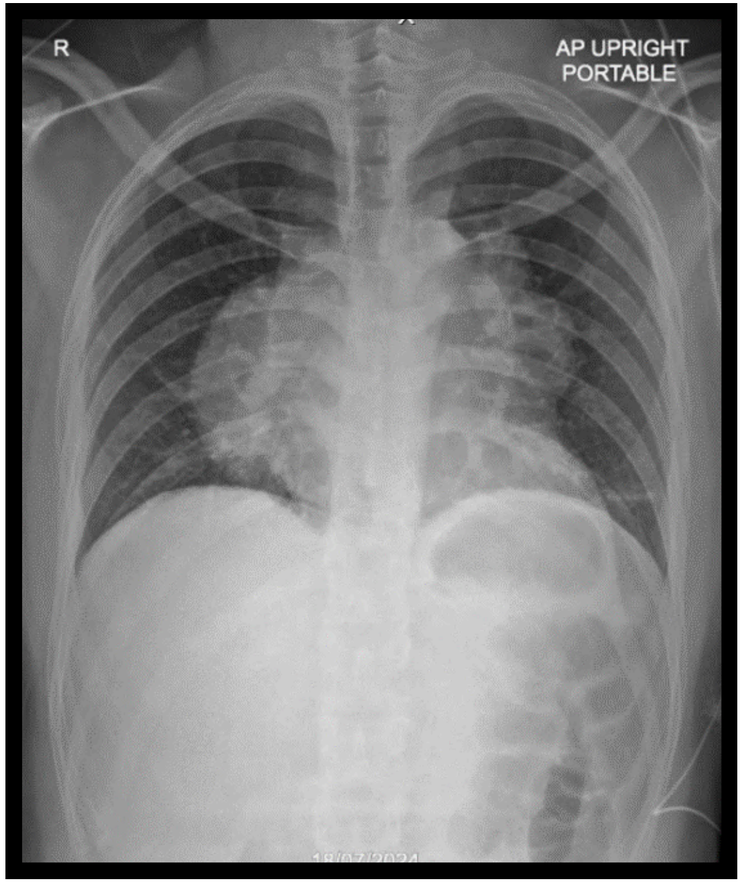
Presentation	Subtypes
Lymphadenopathy	
• Cervical, inguinal , axillary, supraclavicular (most common)	Diffuse large B cell lymphoma (DLBCL), Hodgkin lymphoma, follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, T cell lymphoma (AITL, PTCL, ALCL), etc.
• Mediastinal	Nodular sclerosis Hodgkin lymphoma, primary mediastinal B-cell lymphoma
• Intraabdominal	Burkitt lymphoma, follicular lymphoma, DLBCL
• Spleen	Splenic marginal zone lymphoma, hairy cell leukemia, chronic lymphocytic leukemia/small lymphocytic leukemia, DLBCL

Anterior mediastinal mass

3T + 1L +1P

Clinical features

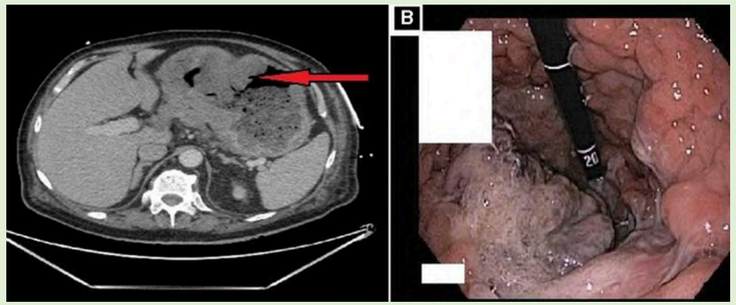
- Dyspnea
- Cough
- Hemoptysis
- Chest pain
- Dysphagia
- Hoarseness
- SVC obstruction



- **Primary mediastinal B-cell lymphoma**
- **Nodular sclerosis classic Hodgkin Lymphoma**
- **T-ALL/LBL**
- T-cell lymphoma (rare)

B-symptom, generalized LN, Marrow failure

Extranodal lymphoma - GI



Common symptoms

- Abdominal pain
- N/V, indigestion
- GI bleed
- B-symptoms
- Gut obstruction (DLBCL)
- Palpable mass (DLBCL)

Common subtypes

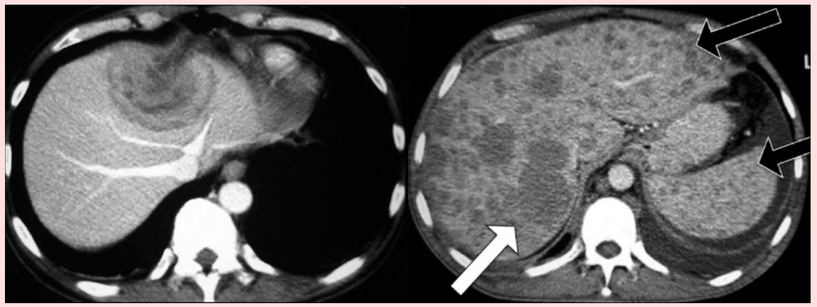
- DLBCL
- MALT - H.pylori
  - ATB
  - RT, R-CVP/CHOP

Common symptoms

- Abdominal pain
- GI bleed
- Gut obstruction
- Palpable mass
- Diarrhea
- B-symptoms

Common subtypes

- DLBCL, BL(iliocecal)
- ENKL, MCL
- MALT, FL
- EATL (T-cell)- aggressive



Common symptoms

- Hepatomegaly
- Jaundice
- RUQ pain
- Palpable mass
- B-symptoms

Common subtypes

- **DLBCL**, BL
- MALT, LPL
- Hepatosplenic TCL

MJ Open Gastroenterology 2019;6:e000320

Extranodal lymphoma - CNS

DLBCL (90%)

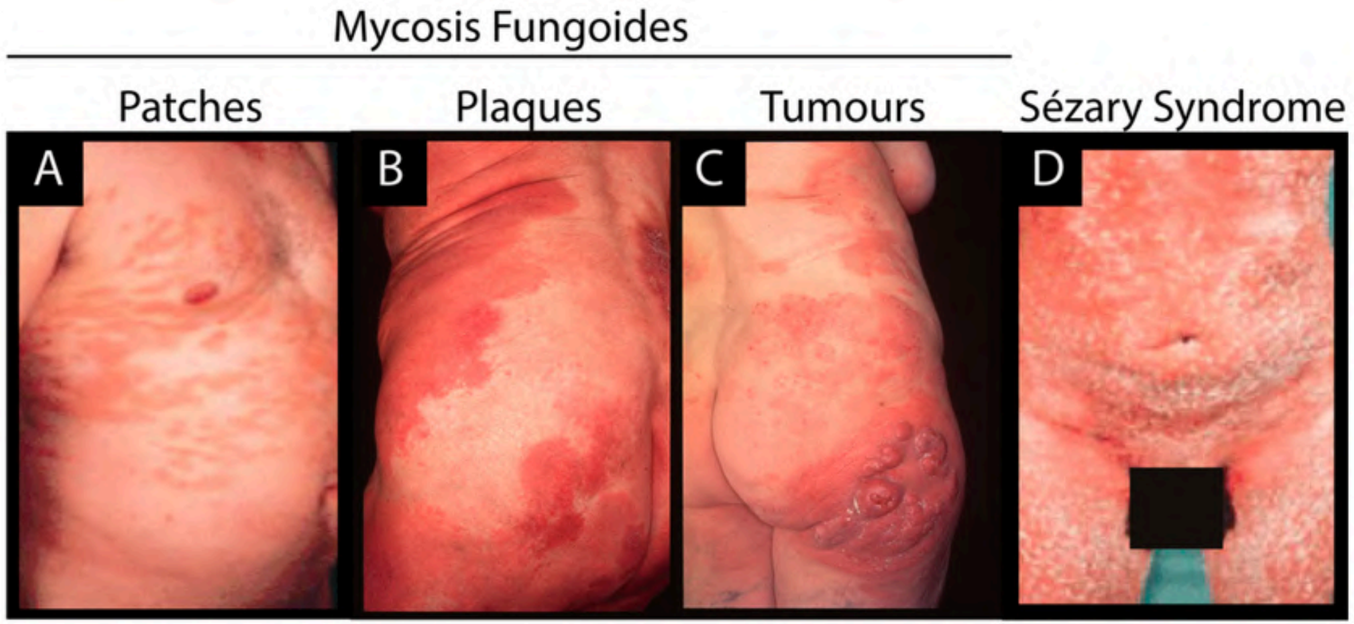
Primary CNS lymphoma

- **S&S** - subacute cognitive impairment, progressive neurological deficits, seizure, increased ICP
- **Risk**
  - Elderly, immunocompromised hosts (HIV)
- **Host**
  - AIDS-defining illness, usually when CD4 < 50 - multiple necrotic lesion (30-70%)
  - Most immunocompetent patients have a solitary brain mass (60-70%)
- **DDx** - CNS infection (toxoplasmosis), tumors
- **Treatment** - HD-MTX-based regimen

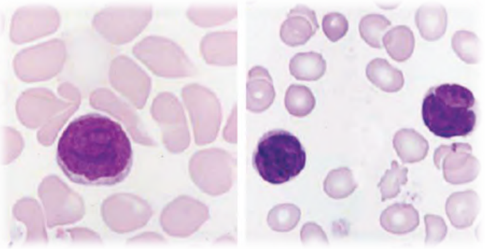
Most arises in frontal lobe, basal ganglia and periventricular regions

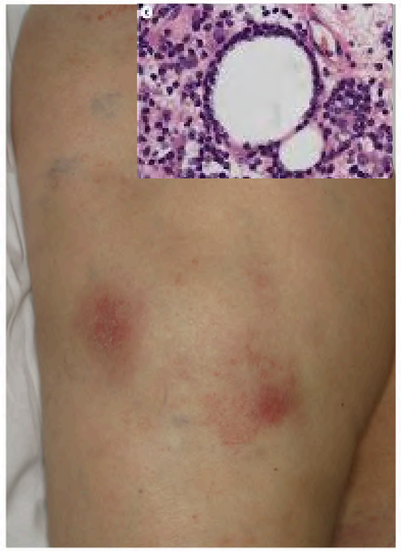
Extranodal lymphoma - Skin

Cutaneous T cell > B cell lymphoma



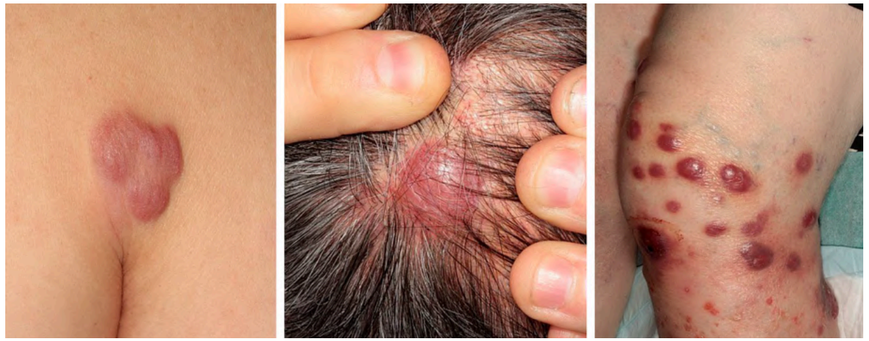
- **S&S**- persistent, itchy, scaly red patches or plaques on sun-protected skin
- **Mx** - skin-directed therapies
  - systemic therapy in advance stage





Subcutaneous panniculitis-like T-cell lymphoma

- Painless
- Erythematous node/plaque
- 20% occur with autoimmune
- DDx lupus panniculitis
- Mx - cyclosporin A



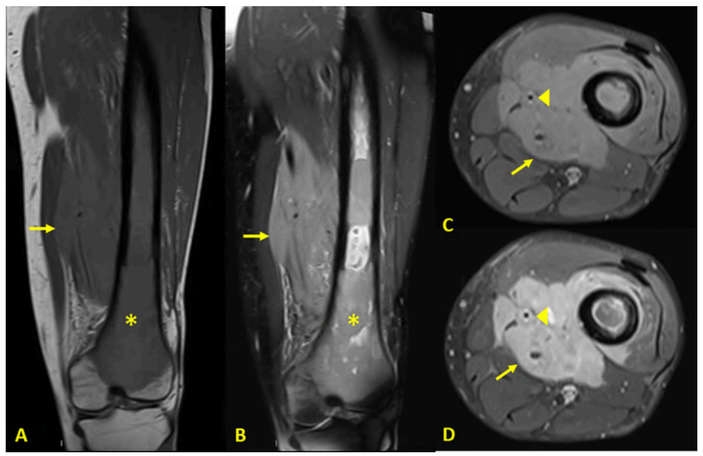
Cutaneous B-Cell Lymphomas

Cancers 2020, 12(6), 1497
J Am Acad Dermatol 2018;79:892-8
Cancers 2020, 12, 1229;

Extranodal lymphoma - bone and soft tissue

- Secondary, advanced » primary (rare)
- **S&S** - bone pain, mass, pathologic fx
- May present with b symptoms, high LDH
- Most common subtype is **DLBCL,** ALCL

	Benign	Malignant
Size	Vary	Usually extensive
Pain	Asymptomatic or mild localized pain	Rest or night pain
Onset	Insidious	Usually rapid
Systemic symptoms	Rare	+/-



MRI: imaging of choice

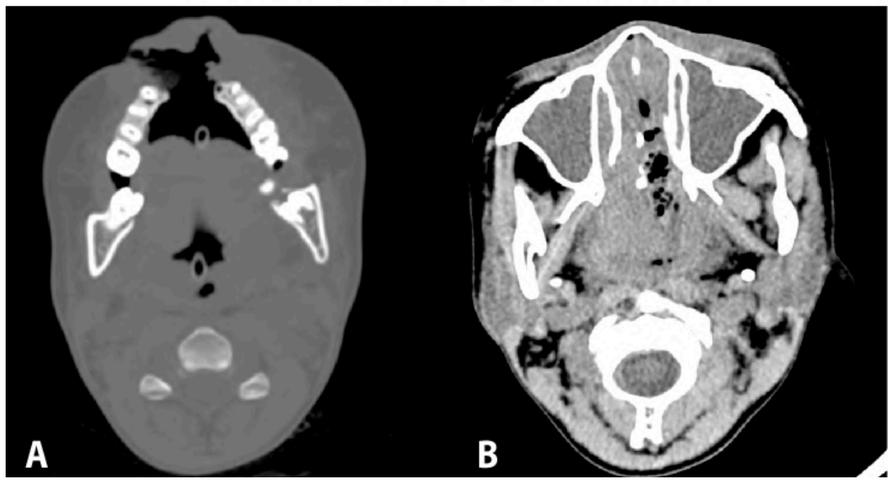
Differential Diagnosis

- Sarcoma (subtypes by age group)
  - Ewing and osteosarcoma - children and young adults
- Multiple myeloma
  - Elderly, involve skull/long bone/pelvis, CRAB, high globulin
- Metastatic tumors
  - Elderly, Specific organ symptoms, high ALP
- Histiocytic disease
  - LCH - DI, lytic lesion at skull/mandible, cystic lung

J Belg Soc Radiol. 2022 Oct 11;106(1):94

Extranodal lymphoma - head and neck

Figure 3. Intraoral view 3 months after initial presentation.



Lethal midline granuloma (LMG)

- progressive necrosis of the nose, palate, and midfacial tissues
- **S&S** - persistent rhinorrhea , foul-smelling nasal discharge, epistaxis, nasal obstruction, chronic pain, erosion

Differential Diagnosis

- **Extranodal NK-Cell Lymphoma CD3+**
  - B-symptom, organ involvement
- Squamous cell carcinoma
- DLBCL **CD20+**
- Mucormycosis
- Wegener granulomatosis

Philipp J Otolaryngol Head Neck Surg 2018; 33 (2): 37-40

Extranodal lymphoma - Effusion

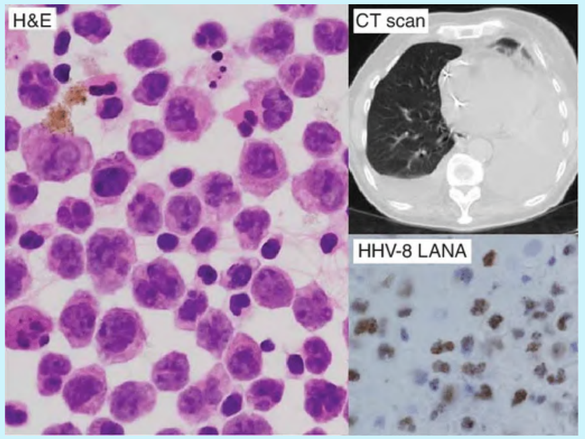
- Ascites, pleural effusion, pericardial effusion

Secondary, advanced > primary (rare)

- Most common subtype is **DLBCL**
- **Mechanisms** – **disease involvement**, **chylous effusion**, lymphatic obstruction, infection
- **Diagnosis** - Fluid cytology, flow cytometry, tissue biopsy
  - Usually **exudative and lymphocytic effusion**
  - **ADA levels are increased** in lymphoma, especially in association with **markedly elevated LDH levels**

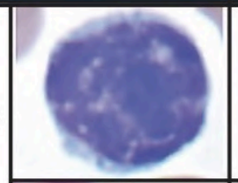
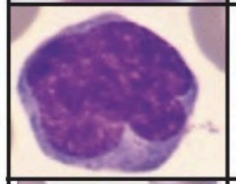
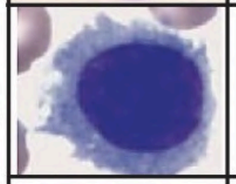
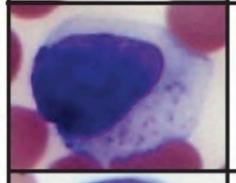
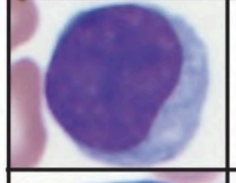
Primary effusion lympnoma

- Rare large B cell NHL
- HIV-related lymphomas
- **S&S** - dyspnea and abdominal distension
- Associated with **HHV-8**
- CD20 negative
- **Mx**- EPOCH, ART



Expert Rev Hematol. 2015 Jun;8(3):343-54.

Leukemic presentation

Figure 2		DIFFERENTIAL DIAGNOSIS		ANCILLARY TESTS
Small, round nuclei →		**CLL** MBL	MCL T-PLL	Flow cytometry CLL FISH panel FISH *CCND1/IGH*
Folded or cleaved nuclei →		**FL** MCL Atypical CLL	T-cell lymphomas Pertussis*	Flow cytometry FISH *CCND1*/IGH, *BCL2* Tissue biopsy
Convoluted nuclei →		**Sézary syndrome** Adult T-cell leukemia		Flow cytometry T-cell clonality
Villous cytoplasm →		HCL **SMZL** HCLV	T-PLL LPL	Flow cytometry *BRAF*
Plasmacytoid →		**LPL** Plasma cell myeloma Plasma cell leukemia		Flow cytometry SPEP/UPEP *MYD88* L265P Myeloma FISH panel
Granules →		**T-LGL** NK cell leukemia		Flow cytometry T-cell clonality KIR profile
Prominent nucleoli →		**T-PLL** B-PLL HCLV MCL		Flow cytometry Cytogenetics
Large cells →		**Burkitt Leukemia** DLBCL MCL ALCL		Flow cytometry FISH *MYC* *CCND1/IGH* *ALK*

Fever of unknown origin

Infection

Immune/inflammation

Malignancy

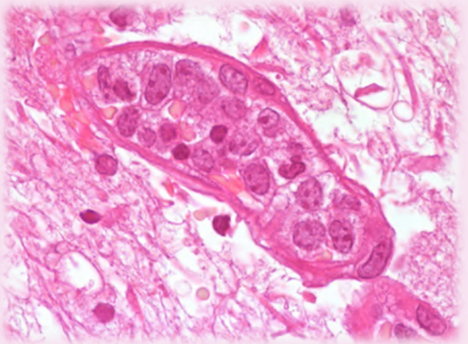
Miscellaneous

Clues for hematologic malignancy

- Lymphadenopathy
- Hepatosplenomegaly
- Cytopenia
- B-symptoms
- High LDH, extremely high ferritin

Intravascular lymphoma

- Large B cells within the lumen of all sized blood vessels
- **S&S** - FUO, B symptom, multiorgan failure, Skin lesion(40%), neurological symptoms(35%), no LN or mass
- **Dx** - random skin biopsy
- **Mx** - R-CHOP



Blood (2018) 132 (15): 1561–1567.

Approach to lymphoma

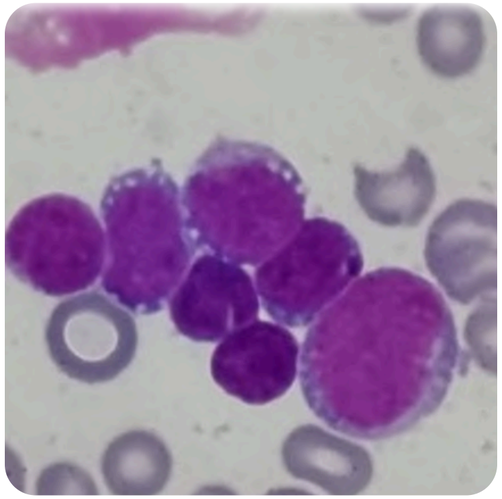
- **Clinical presentation**
  - Lymphadenopathy
  - Extra nodal manifestation
  - Fever of unknown origin
  - Cytopenia
  - Lymphocytosis
  - Hepatosplenomegaly
  - Metabolic disturbance
- **Clinical course**
  - Indolent (> 6-12 months)
  - Aggressive (< 3-6 months)

- **Tissue diagnosis**
  - HL or NHL
  - B or T/NK cell
- **Staging**
  - Ann Arbor or Lugano staging
- **Prognosis score**
  - Clinical, CBC, blood chemistry, genetic and molecular profiles
- **Treatment**
  - Curative or palliative
  - Fit or non fit
- **Evaluate response of treatment**

Diffuse large B-cell lymphoma (DLBCL)

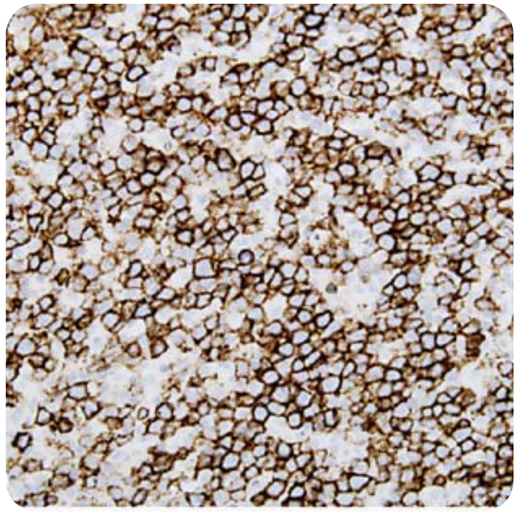
Clinical

- Rapidly enlarging LN
- Extra nodal
- B symptoms
- 2/3 advanced disease

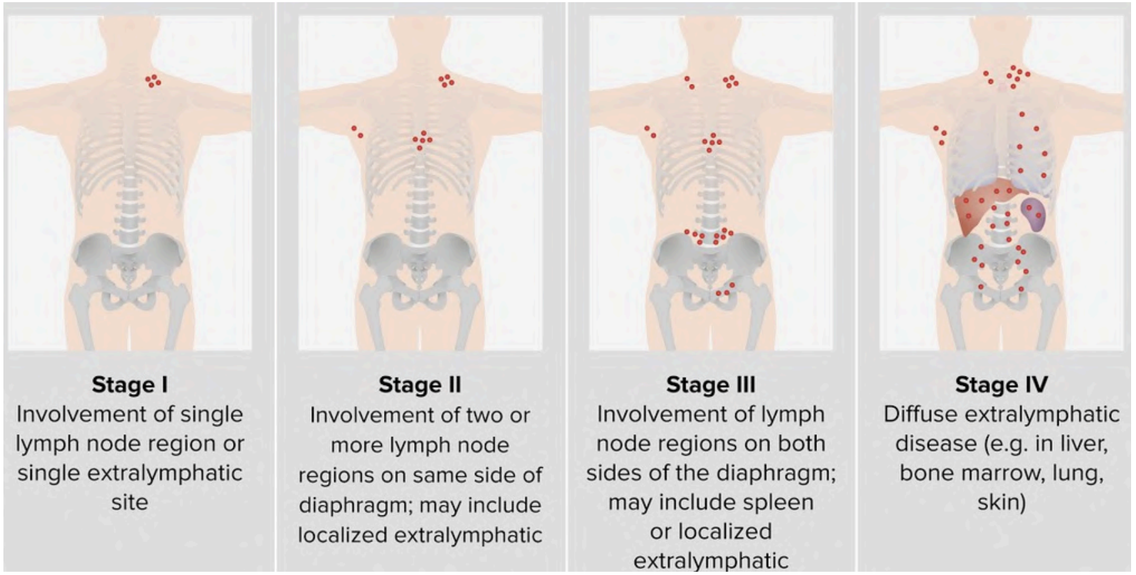


IPI or R-IPI

- **Age** > 60 years old
- **Ann Arbor staging** III/IV
- **ECOG PS** > 1
- **LDH** > 1X
- **Extra-nodal site** > 1



Pan–B-cell markers
(CD19, CD20, CD22, CD79a, PAX5)



Treatment

- R-CHOP

Treatment of aggressive lymphoma

Hodgkin lymphoma

- ABVD, Escalated dose BEACOPP, Anti-CD30+AVD, checkpoint inhibitors+AVD

Diffuse large B cell lymphoma

- R-CHOP

Mantle cell lymphoma

- R-CHOP/R-DHAP, R-bendamustine

Burkitt lymphoma

- Dose-adjusted EPOCH-R, CODOX-M/IVAC, Hyper-CVAD

Peripheral T-cell lymphoma

- CHOP, CHOP + Etoposide, anti-CD30+CMT

Cutaneous T-cell lymphoma

- Skin directed therapy, chemotherapy

Indolent lymphoma

- Follicular lymphoma (FL)
- CLL/SLL
- Marginal zone lymphoma (MZL)
- Lymphoplasmacytic lymphoma
- Indolent Mantle cell lymphoma

Marginal zone lymphoma (MZL)

- Extranodal MZL (EMZL) or MALT lymphoma (70%)

chronic antigenic stimulation by infectious pathogens or autoimmunity

MALT lymphoma	Associated with	Sign and symptoms
Gastric	*Helicobacter pylori*	Epigastric pain, dyspepsia, weight loss, GI bleed
Salivary gland	Sjögren syndrome	Slow growing masses
Thyroid	Hashimoto thyroiditis	Slow growing masses
Orbital	*Chlamydophila psittaci*	Slow growing masses or eye redness
Skin	*Borrelia burgdorferi*	Violaceous skin papules, plaques or nodules
Lungs	*Achromobacter xylosoxidans*	Incident findings of lung nodules

- Nodal MZL (NMZL) (20%)
  - Asymptomatic with lymphocytosis, painless lymphadenopathy
  - Treatment same as follicular lymphoma when clinically indicated
- Splenic MZL (SMZL) (10%)

Treatment of indolent lymphoma

Localized disease

- Targeting infectious agents
  - *H.pyroli* eradication in Gastric MZL
- RT
- Rituximab, CIT
- Watch and wait

Table 1. Indications for treatment in low grade lymphoma.

Indication	Detail
High tumor burden [10]	Any site ＞7 cm Three or more sites ＞3 cm Splenomegaly (＞16 cm) Pleural or peritoneal effusion Circulating tumor cells ＞5,000/μL Cytopenia secondary to lymphoma - Absolute neutrophil count ＜1,000/μL - Platelet count ＜100,000/μL
Disease-related symptoms	Fever Night sweats Weight loss Compression Other lymphoma-related symptoms
Steady progression	Over at least 6 months

Advanced disease

- Watch and wait (without treatment indication)
- Chemoimmunotherapy (R-CVP, R-CHOP, R-bendamustine in B-NHL)

Blood Res 2022;57:S120-S129.

Case

Case 1 : Splenomegaly

Patient: Male, 52-year-old

Chief Complaint: abdominal fullness for 6 month and weight loss

PE: tip of spleen at umbilicus

Clinical Focus: massive splenomegaly

Differential diagnosis

- Chronic myeloid leukemia
- Primary myelofibrosis
- Splenic indolent lymphoma
- CLL

Case 2: BMF with huge splenomegaly

Patient: Male 46-year-old

Chief Complaint: Abd fullness and LUQ pain with BMF for 1 month

PE: tip of spleen at umbilicus

Differential diagnosis

- Aggressive NHL (DLBCL)
- Splenic indolent lymphoma with disease progression or large cell transformation
- CML with blast phase
- PMF with blast phase
- CLL with Richter's Transformation

Approach to splenomegaly

- **Infection response**
  - brucellosis, tuberculosis, histoplasmosis, toxoplasmosis, malaria, leishmaniasis, infectious mononucleosis (EBV), HIV, CMV
- **Myeloproliferative neoplasm**
  - PMF, CML, PV, CMML
- **Lymphoma and leukemia**
  - NHL (DLBCL, SMZL, HCL, LPL, LGL, CLL), advanced HL, ALL, AML M4-5,
- **Hemolytic anemia**
  - HS, congenital or acquired hemolytic anemias, hemoglobinopathies, AIHA
- **Autoimmune and inflammatory diseases**
  - RA(Felty), SLE, sarcoidosis
- **Congestive**
  - cirrhosis, hepatic/portal/splenic vein thrombosis, congestive heart failure, hepatic schistosomiasis
- **Infiltrative**
  - Gaucher, amyloidosis
- **Tumor**
  - hemangioma, sarcoma, metastasis (melanoma, breast)
- **Histiocytic disorder**
  - HLH

Massive splenomegaly

More than 8 cm below LCM or weight >1,000 g or >20 cm

Lymphoma

- **Splenic lymphoma**
  - common **-** HCL, SMZL, T-LGL
  - uncommon - DLBCL, FL, MCL
- Chronic lymphocytic leukemia

MPN

- **Chronic myeloid leukemia**
- **Primary myelofibrosis**
- Polycythemia vera (rare)

Infection

- Malaria, leishmania

Infiltrative disease

- Gaucher's disease

Hyperfunction

- Thalassemia major

NEJM 391;14
ASH

Common lymphoma types with huge splenomegaly

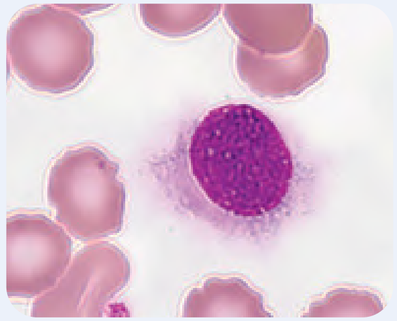
Hairy-Cell Leukemia

- Rare, indolent B-NHL
- Median age 55-60 years
- Cytopenias
- Splenomegaly (80%) - huge
- Rare constitutional symptoms
- Less extramedullary sites

4 : 1

BRAF V600E mutation

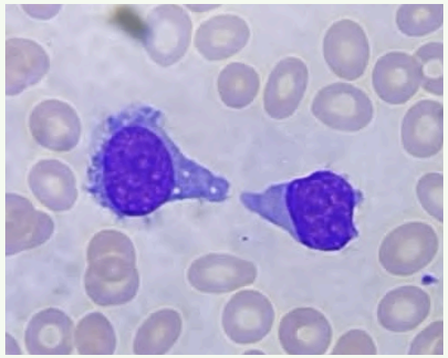
Cytopenia with low leukemic cell counts but leukocytosis (10 to 15%)



Treat when symptomatic
Cladribine or pentostatin

Splenic MZL

- Rare, indolent B-NHL
- Massive splenomegaly and BM involvement with minimal or absent lymphadenopathy
- Lymphocytosis
- 20% - autoimmune (AIHA)
- 25% cytopenia from hypersplenism
- B symptoms - uncommon



Treat when symptomatic
Rituximab, CMT, splenectomy

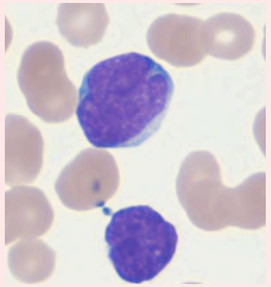
DLBCL

- Advanced > primary
- B-symptoms - typical
- Middle age to older adults

R-CHOP

Mantle cell lymphoma

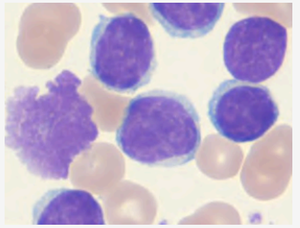
- Aggressive B-NHL
- Usually advanced
- Hepatosplenomegaly
- Generalized LN
- B-symptoms - 40%
- Older adults (median 70 years)



R-CHOP/R-DHAP, R-Bendamustine

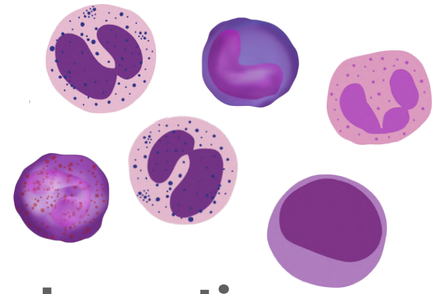
CLL

- Advanced stage
- Lymphocytosis
- Generalized LN



Treat when symptomatic
CMT, BTKi, BCL2i

Chronic myeloid leukemia



CML is myeloproliferative neoplasm which characterized by a balanced genetic translocation, t(9;22)(q34.1;q11.2), containing BCR-ABL1 fusion gene

Common clinical features

- 50% are asymptomatic
- Fatigue, malaise, weight loss
- Anemia
- Splenomegaly - huge (easy satiety, LUQ pain)

Rare manifestations

- Bleeding (platelet dysfunction)
- Gout (hyperuricemia)
- Visual disturbance (hemorrhage, leukemic)
- Thrombosis
- Leukostatic symptoms
- Priapism

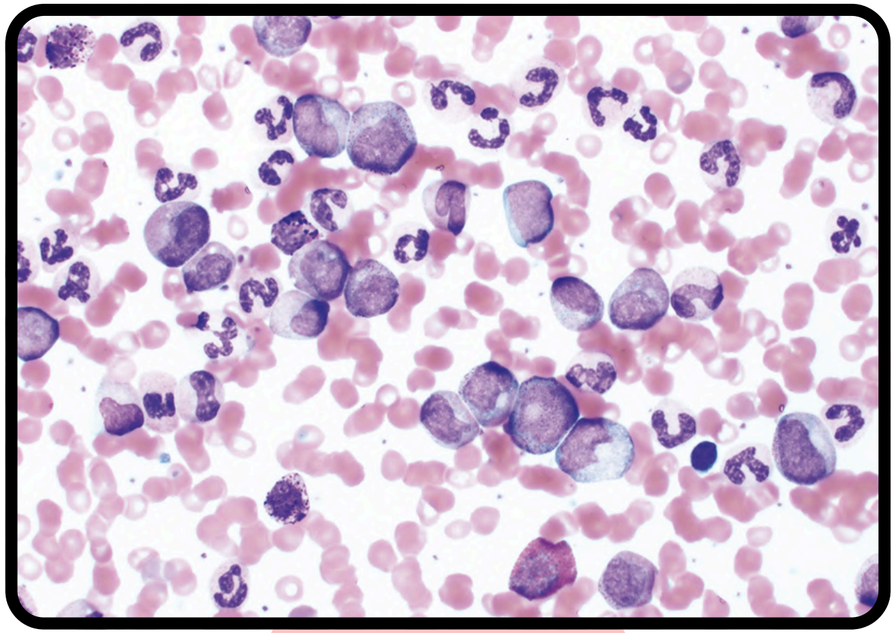
When to consider CML Blast phase

- Lymphadenopathy
- Infiltration of skin or other tissues
- Bone pain
- Pain from splenic infarction
- Headache
- Fever
- Bleeding from thrombocytopenia

Chronic myeloid leukemia

Diagnosis

- Persistent unexplained neutrophilic leukocytosis (or occasionally thrombocytosis)
- Presence of the Philadelphia (Ph) chromosome abnormality, t(9;22)(q34;q11), by routine cytogenetics, or Ph-related molecular BCR::ABL1 abnormalities by FISH or by molecular studies



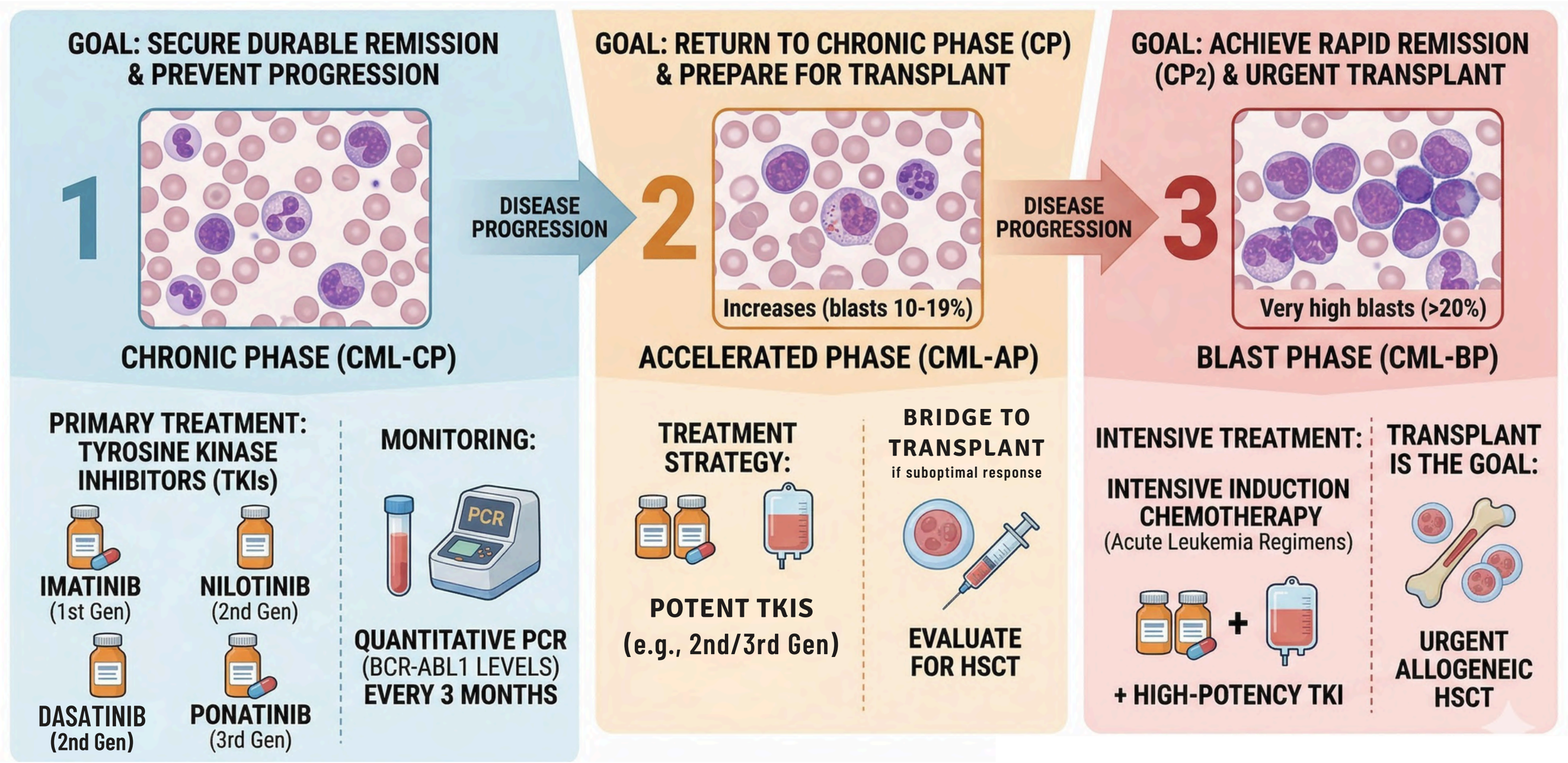
CBC with PBS

BMA & BM Biopsy

Cytogenetic Analysis

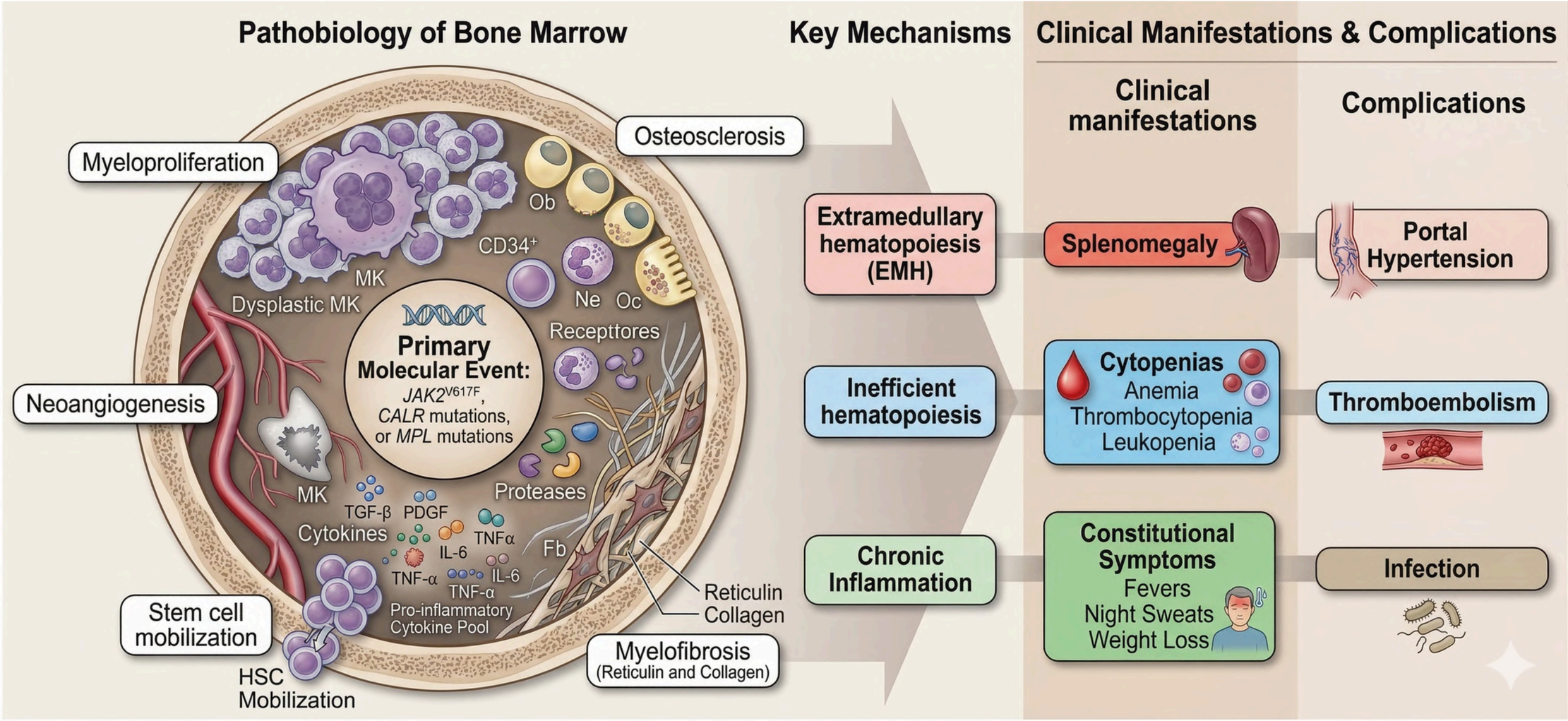
RT-PCR/FISH for BCR-ABL

Treatment of CML



Am J Hematol. 2024;99:2191–2212.
Curr Hematol Malig Rep. 2023 Dec;18(6):234-242.

Primary myelofibrosis



International Journal of General Medicine 2014:7 89–101

Clinical manifestation of PMF

Common clinical features

- Asymptomatic (30%)
- Severe anemia (Overt)
- Marked hepatosplenomegaly
- Constitutional symptoms (fatigue, night sweats, fever)
- Cachexia

Other manifestations

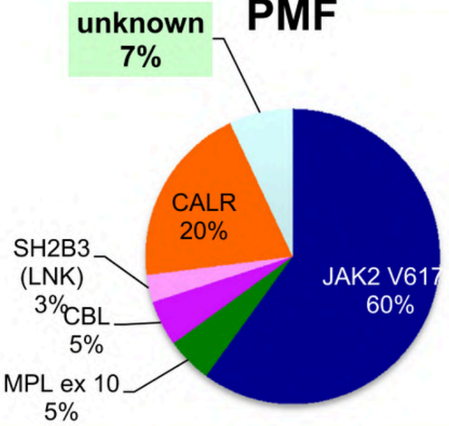
- Non hepatosplenic EMH
- Bone pain
- Splenic infarction (Overt)
- Pruritus
- Portal hypertension
- Thrombosis (splanchnic)
- Bleeding
  - AvWS (Pre-fibrotic)
  - Low platelet, varices (Overt)

Am J Hematol. 2023;98:801–821.
International Journal of General Medicine 2014:7 89–101

Non-hepatosplenic EMH

- **Cord compression**
- **Pleural effusion, hemothorax**
- **Generalized lymphadenopathy**
- Ascites
- Skin manifestation
- GI obstruction
- Obstructive uropathy

Primary myelofibrosis



Primary myelofibrosis (Overtly fibrotic stage) (*Diagnosis requires meeting all 3 major criteria and one minor criterion*)	Primary myelofibrosis (Pre-fibrotic/early stage) (*Diagnosis requires meeting all 3 major criteria and one minor criterion*)
Major criteria: 1. Megakaryocyte proliferation and atypia,[a] accompanied by ≥grade 2 reticulin/collagen fibrosis[b] 2. Presence of *JAK2*, *CALR* or *MPL* mutations, or presence of other clonal markers, or absence of evidence for reactive bone marrow fibrosis 3. Not meeting ICC criteria for other myeloid neoplasms	***Major criteria***: 1. Megakaryocyte proliferation and atypia,[a] accompanied by ≤grade 1 reticulin/collagen fibrosis, granulocyte proliferation/ decreased erythropoiesis 2. Presence of *JAK2*, *CALR* or *MPL* mutations, or presence of other clonal markers, or absence of evidence for reactive bone marrow fibrosis 3. Not meeting ICC criteria for other myeloid neoplasms
Minor criteria: *Anemia not otherwise explained* *Leukocytosis* $\geq 11 \times 10^9/L$ *Palpable splenomegaly* *Increased serum lactate dehydrogenase* *A leukoerythroblastic blood smear*	***Minor criteria***: *Anemia not otherwise explained* *Leukocytosis* $\geq 11 \times 10^9/L$ *Palpable splenomegaly* *Increased serum lactate dehydrogenase*

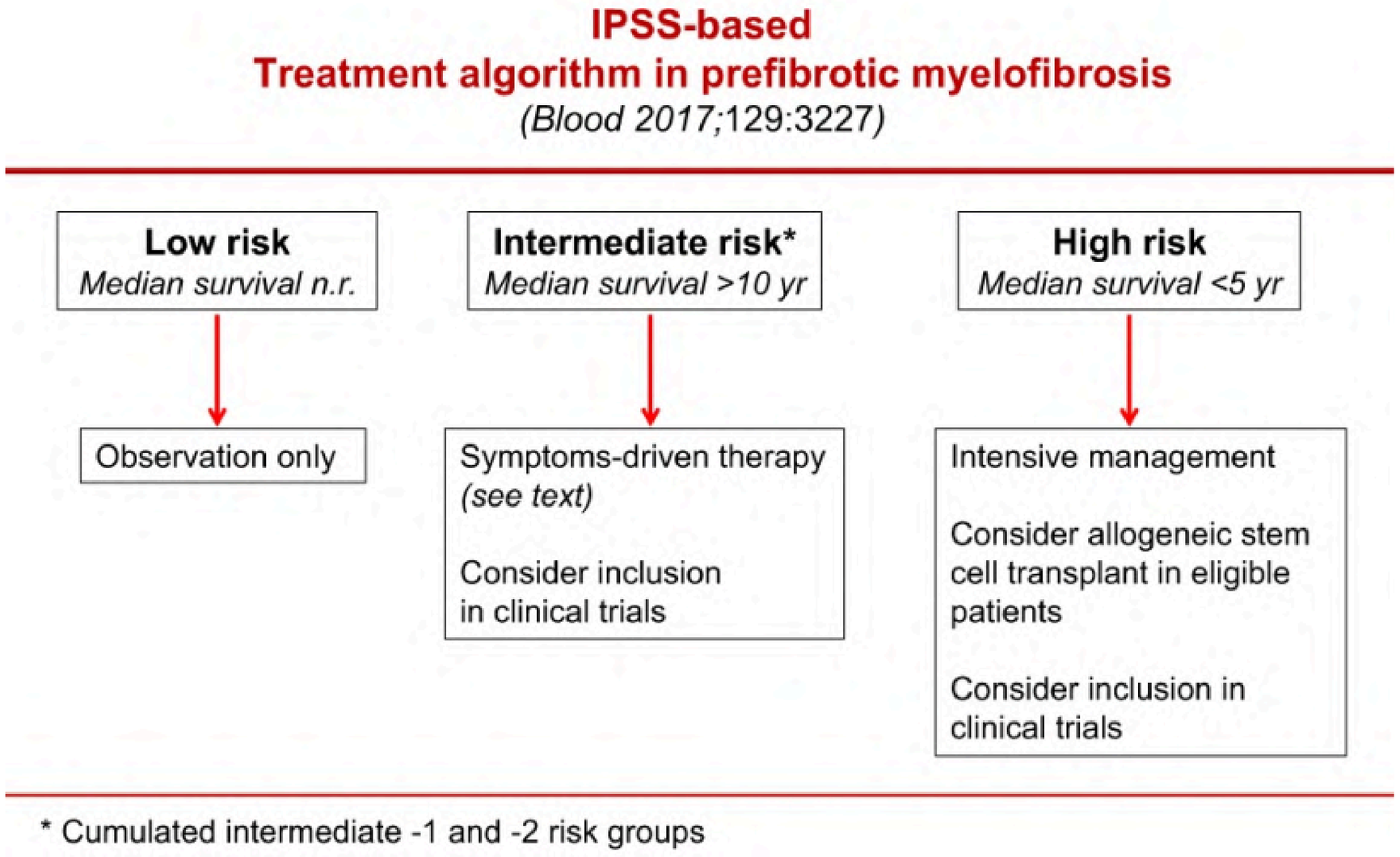
Am J Hematol. 2023;98:801–821.
International Journal of General Medicine 2014:7 89–101

Risk stratification of PMF

Models	Variables	Risk categories					
		Very low	Low	Intermediate-1	Intermediate-2	High	Very high
IPSS[d] *International Prognostic Scoring System*	Age >65 years (1 point) Constitutional symptoms[a] (1 point) Hemoglobin <10 g/dl (1 point) Leukocytes >25 × 10(9)/L (1 point) Circulating blasts ≥1% (1 point)	**NA**	(0 points) 11.3 years	(1 point) 7.9 years	(2 points) 4 years	(≥3 points) 2.3 years	**NA**
DIPSS[e] *Dynamic International Prognostic Scoring System*	Age >65 years (1 point) Constitutional symptoms (1 point) Hemoglobin <10 g/dl (2 points) Leukocytes >25 × 10(9)/L (1 point) Circulating blasts ≥1% (1 point)	**NA**	(0 points) Not reached	(1–2 points) 14.2 years	(3–4 points) 4 years	(5–6 points) 1.5 years	**NA**
DIPSS-plus[e]	Age > 65 years (1 point) Constitutional symptoms[a] (1 point) Hemoglobin <10 g/dl (1 point) Leukocytes >25 × 10(9)/L (1 point) Circulating blasts ≥1% (1 point) Unfavorable karyotype[h] (1 point) Platelet count <100 × 10(9)/L (1 point) Transfusion needs (1 point)	**NA**	(0 points) 15.4 years	(1 point) 6.5 years	(2–3 points) 2.9 years	(≥4 points) 1.3 years	**NA**

Am J Hematol. 2023;98:801–821.

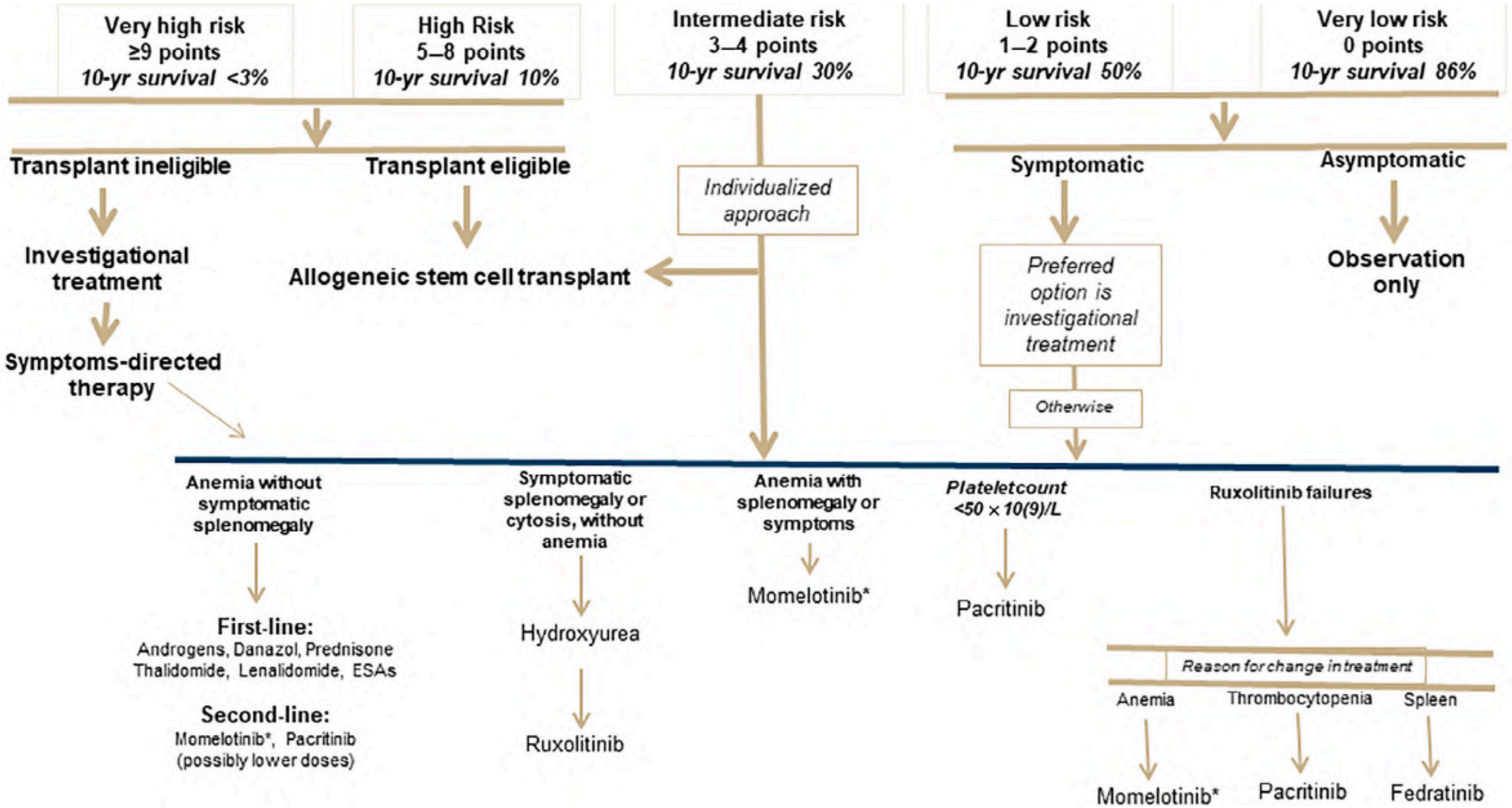
Treatment of PMF



Am J Hematol. 2023;98:801–821.

Treatment of PMF

Mutation-enhanced international prognostic scoring system, version 2.0. (MIPSSv2)
Karyotype: Very high risk 4 points; unfavorable 3 points;
Mutations:: ≥2 high risk mutations 3 points; one high risk mutation 2 points;
Type 1 CALR mutation: absent 2 points;
Clinical risk factors: constitutional symptoms 2 points; severe anemia 2 points; moderate anemia 1 point; ≥2% circulating blasts 1 point



Am J Hematol. 2023;98:801–821.

Case

Case 1: Splanchnic Thrombosis

Patient: Female, 52-year-old

Presentation: Abdominal pain and jaundice for 2 days.

Clinical Focus: Splanchnic Thrombosis

- Involves clots in the portal, splenic, or mesenteric veins.
- Often presents with acute abdominal symptoms and can lead to hepatic dysfunction.
- Frequently associated with myeloproliferative neoplasms (MPNs) or other hypercoagulable states.

Case 2: Stroke in the Young

Patient: Male, 32-year-old

Presentation: Sudden hemiparesis for 6 hours.

Clinical Focus: Stroke in the Young

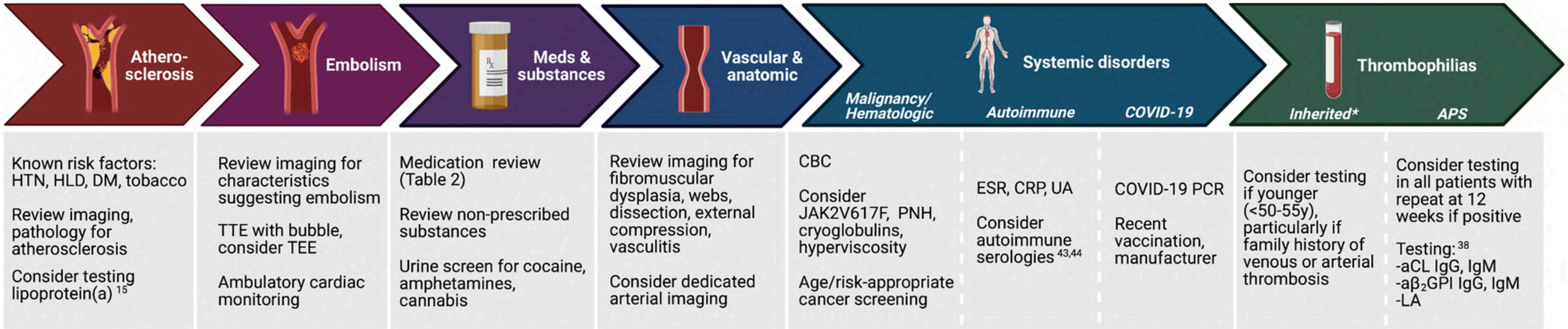
- Defined as an acute ischemic or hemorrhagic event in patients under 45
- Potential etiologies include PFO (Patent Foramen Ovale), arterial dissection, or underlying hematologic disorders.

Arterial thrombosis

- Most common sites - ischemic stroke, myocardial infarction
- Other sites
  - Retinal arterial occlusion - monocular, sudden, painless, visual loss
  - Splenic infarction - left-sided abdominal pain
    - cause - thromboembolic, infiltrative hematologic disease
  - Renal artery infarction - sudden abdominal/flank pain, AKI, hematuria
    - 60-70% from atrial fibrillation
  - Intestinal infarction - abdominal pain, LGIB
  - Peripheral artery occlusion - symptoms depend on which artery is blocked
    - most common cause - atherosclerosis

Hematology Am Soc Hematol Educ Program (2021) 2021 (1): 76–84.

Arterial thrombosis



PFO
AF

Stroke
MI
PA

JAK2, PNH – splenic, intraabdominal

FMD – stroke, renal (HT)

CRAO – GCA, PAN, SLE

Renal – medium to large vss vasculitis (RPGN, HT, RAS)

Young (<50-55)
Family history
Recurrent pregnancy loss

Hematology Am Soc Hematol Educ Program (2021) 2021 (1): 76–84.

Venous thrombosis

- Most common sites - pulmonary embolism, DVT at lower limbs
  - Cerebral venous sinus thrombosis (CVST)
    - headache(90%, insidious), increased ICP(N/V, papilledema), seizure
  - Splanchnic vein thrombosis (SVT)
    - Hepatic vein - hepatomegaly, RUQ pain, ascites, jaundice
    - Portal vein - asymptomatic, acute(abdominal pain, ascites), chronic(PHT, UGIB)
    - Splenic vein - acute(abdominal pain), chronic(UGIB, splenomegaly)
    - Mesenteric vein - acute (diffuse abdominal pain, N/V)
  - Upper extremity DVT (UEDVT) - limb swelling
  - Renal vein thrombosis (RVT) - flank pain, renal dysfunction, hematuria
  - Others : retinal, ovarian vein thrombosis

Blood. 2020;135(5):326-334

Approach to venous thrombosis

Hereditary	Acquired
• Factor V Leiden / Activated protein C resistance • Prothrombin *G20210A* mutation • Antithrombin deficiency • Protein C deficiency • Protein S deficiency • Hyperhomocysteinemia • Elevated factor VIII	• Surgery, trauma, immobility, hospitalization, indwelling catheter • High estrogen state, pregnancy • Malignancy • Myeloproliferative neoplasm • Antiphospholipid syndrome • Paroxysmal nocturnal hemoglobinuria • SLE/collagen vascular disease • Inflammatory bowel disease • Nephrotic syndrome • Obesity

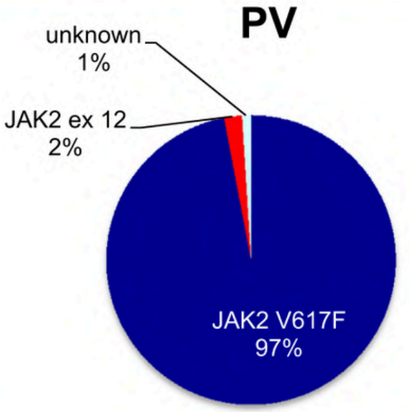
Blood. 2020;135(5):326-334

Venous thrombosis

Splanchnic vein thrombosis	**Liver cirrhosis**, **MPN(JAK2 V617F mutation)**, PNH, Behçet's disease, IBD, thrombophilia or abdominal cancers/inflammation
Cerebral venous sinus thrombosis	**OCP, pregnancy, hormone** APS, JAK2, malignancy, autoimmune
Upper extremity DVT	**Paget-Schrotter syndrome or Thoracic outlet syndrome** CVCs, malignancy
Renal vein thrombosis	**Cancer (66%), nephrotic syndrome (20%)** , others

Blood. 2020;135(5):326-334

Polycythemia vera



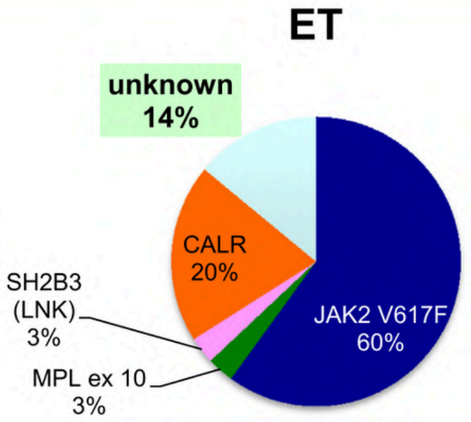
- JAK2-mutated MPN
- Clonal erythrocytosis
- Leukocytosis, thrombocytosis
- Splenomegaly (30%)
- Microcirculatory disturbances
- **Increased risk of thrombosis**
- Progression into myelofibrosis or AML (incidence of sAML after 10 years is ~2%)

Major criteria:
1. Hemoglobin >16.5 g/dL in men or > 16 g/dL in women; or hematocrit >49% in men or > 48% in women or increased red blood cell mass
2. Bone marrow biopsy showing age-adjusted hypercellularity with trilineage growth (panmyelosis) with pleomorphic mature megakaryocytes
3. Presence of JAK2 mutation (JAK2V617F or JAK2 exon 12 mutation)
Minor criterion:
1. Subnormal serum erythropoietin level
All 3 major criteria or the first 2 major and the minor criterion

Am J Hematol. 2023 Sep;98(9):1465-1487
Clin Lymphoma Myeloma Leuk. 2014 Sep;14 Suppl:S23-35

Essential thrombocythemia

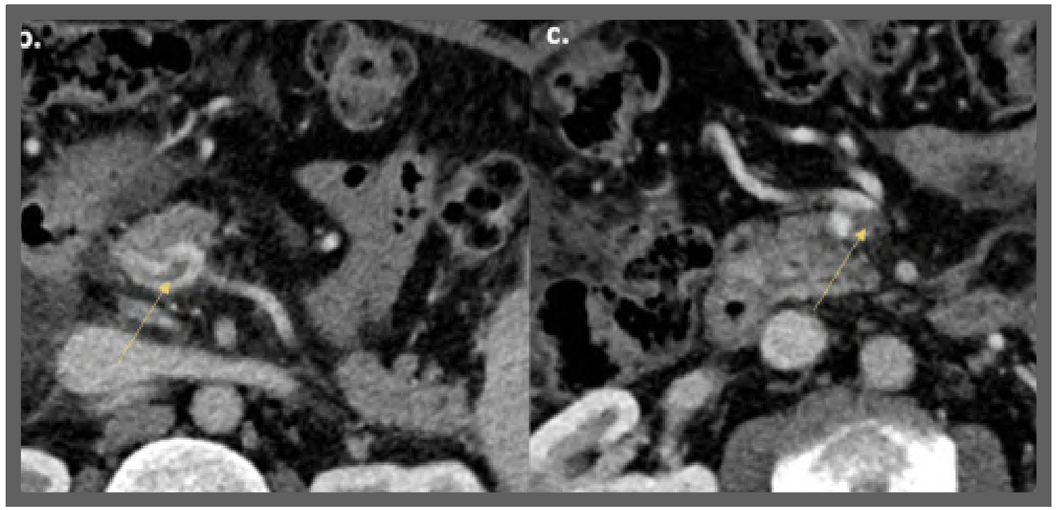
- JAK2 mutation-prevalent MPN
- Clonal thrombocytosis
- **Clinical course - indolent**
- Thrombotic or hemorrhagic complications
- Microcirculatory symptoms
- less frequently, by disease transformation into MF or AML (incidence of sAML is ~1% after 10 yrs)



Major criteria:
1. Platelet count ≥ 450 × 10^9/L
2. Bone marrow biopsy showing megakaryocyte proliferation and loose clusters
3. Not meeting WHO criteria for other myeloid neoplasms(CML, PV, PMF, MDS etc.)
4. JAK2/CALR/MPL mutated
Minor criterion:
1. Other clonal marker present
2. No evidence of reactive thrombocytosis
All 4 major criteria or the first 3 major and the minor criterion

Am J Hematol. 2024;99:697–718.
Clin Lymphoma Myeloma Leuk. 2014 Sep;14 Suppl:S23-35

Clinical manifestation of PV and ET



- Asymptomatic
- Erythromelalgia
- Headaches, lightheadedness
- Visual symptoms - blurring
- Pruritus (more typical in PV)

Thrombotic events (25%)

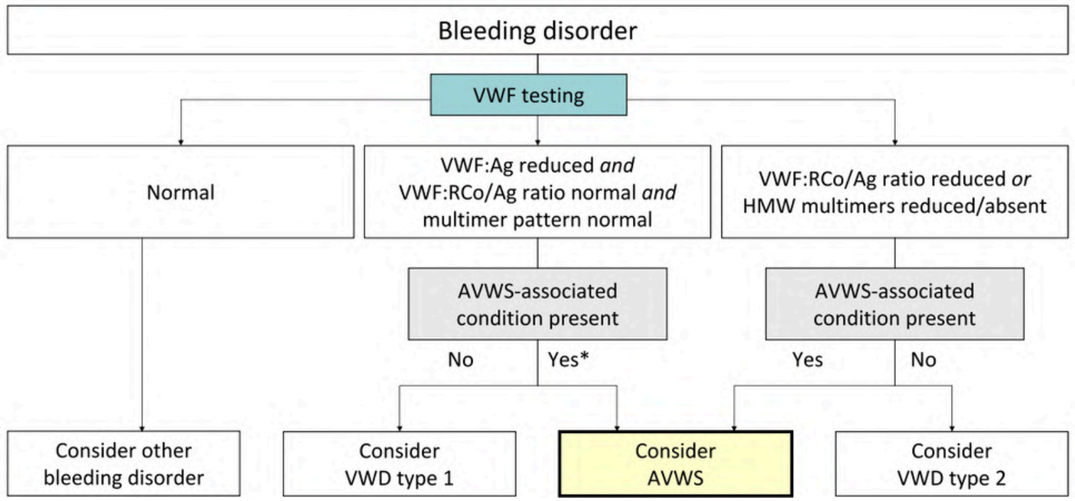
- arterial (15%) - stroke, MI, PAD
- venous (8%) - DVT, PE, unusual sites - rare (CVST, splanchnic)

Cureus. 2023 Sep 19;15(9):e45527.
Hematology Am Soc Hematol Educ Program. 2012;2012:571-581.

Clinical manifestation of PV and ET

- Splenomegaly (rare case with huge splenomegaly)
- In case of extremely high platelet (> 1,000,000),
  - mucocutaneous bleeding
  - major hemorrhage (GI bleeding)

Acquired von Willebrand syndrome

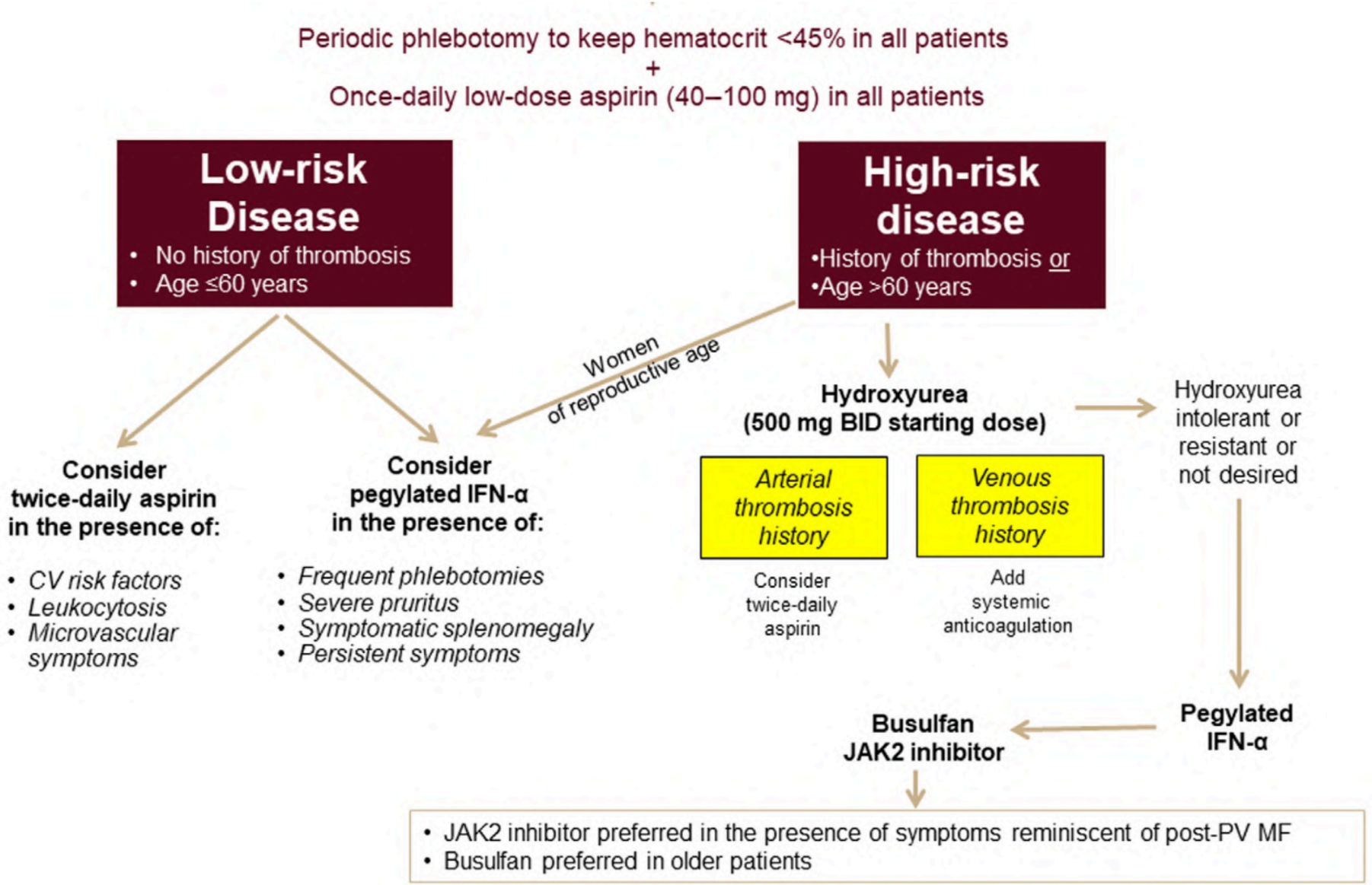


Other cause - LPD, MM, autoimmune

Mx - DDAVP, vWF/FVIII concentrates, antifibrinolytics

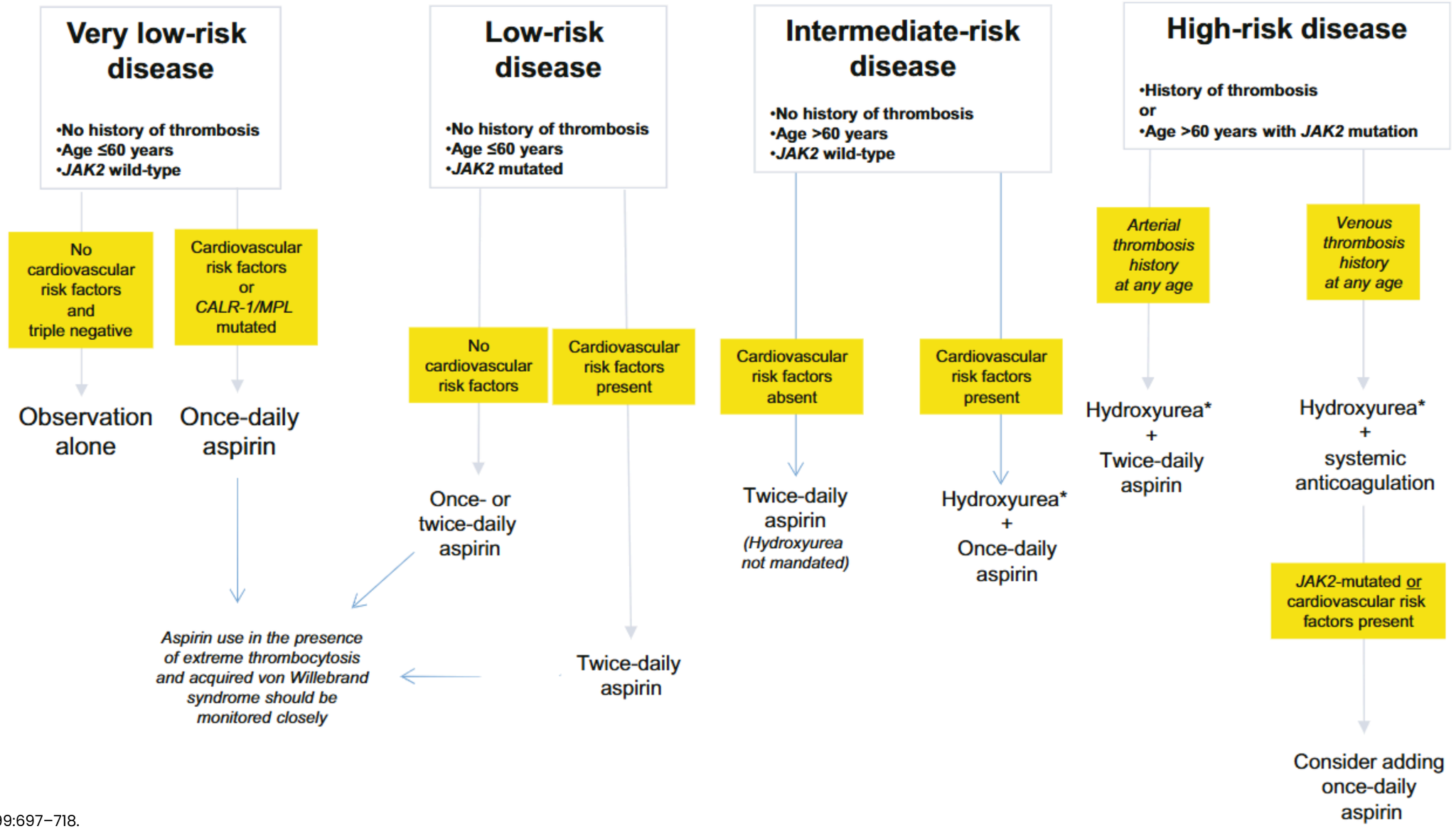
Cureus. 2023 Sep 19;15(9):e45527.
Hematology Am Soc Hematol Educ Program. 2012;2012:571-581.

Treatment of polycythemia vera



Am J Hematol. 2023;98:1465–1487

Treatment of Essential thrombocythemia



Am J Hematol. 2024;99:697–718.

Case

Case 1: Cord compression

Patient: Male 66-year-old

Chief Complaint: paraparesis for 1 week

Clinical focus: spinal cord syndrome

Case 2: Visual impairment

Patient: Male 68-year-old

Chief Complaint: blurred vision for 1 week

Clinical focus: binocular or monocular

- Anterior or posterior pathway
- Other signs and symptoms

Case 3: Nephrotic syndrome

Patient: Female, 58-year-old

Chief Complaint: foamy urine for 2 months

Clinical focus: nephrotic syndrome

- Medical history
- Other sign and symptoms

Case 4: Polyneuropathy

Patient: Male, 74-year-old

Chief Complaint: progressive numbness and weakness at both extremities for 1 year

Clinical focus: polyneuropathy

- Medical history and other signs and symptoms

Monoclonal gammopathy (paraprotein)

- **Plasma cell neoplasms and other diseases (common)**
- **B-cell neoplasm**
  - Lymphoplasmacytic lymphoma
  - Low grade B-cell lymphoma
  - DLBCL

Plasma cell neoplasms and other diseases with paraproteins

- *Monoclonal gammopathies*
  - Cold agglutinin disease
  - IgM MGUS
  - Non-IgM MGUS
- MGRS
- *Diseases with monoclonal immunoglobulin deposition*
  - AL amyloidosis
  - MIDD
- *Heavy chain diseases*
- *Plasma cell neoplasms*
  - Plasmacytoma, multiple myeloma
  - POEMS syndrome; TEMPI syndrome; AESOP syndrome

Neurologic

Demyelinating – CANOMAD, POEMS
anti-MAG NP
Axonal – amyloidosis, cryoglobulinemia

Renal

proteinuria,
microscopic hematuria
HT, renal insufficiency

Dermatologic

cryoglobulinemia, amyloidosis,
Schnitzler syndrome

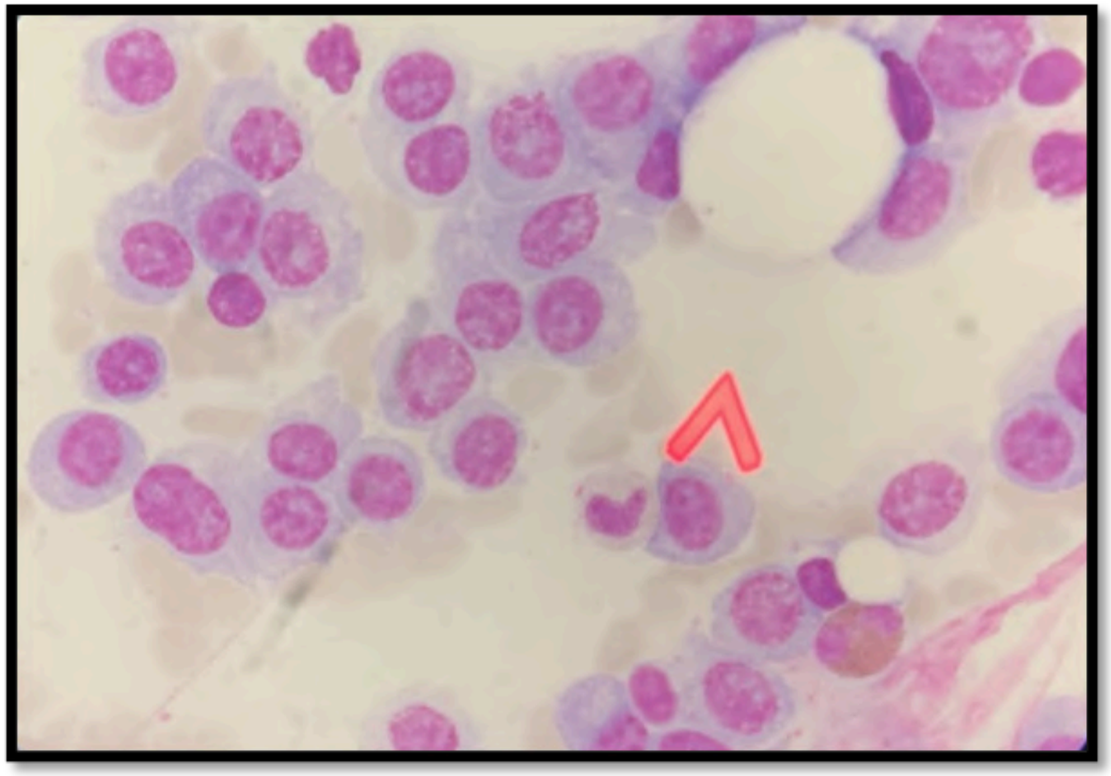
Multiple myeloma

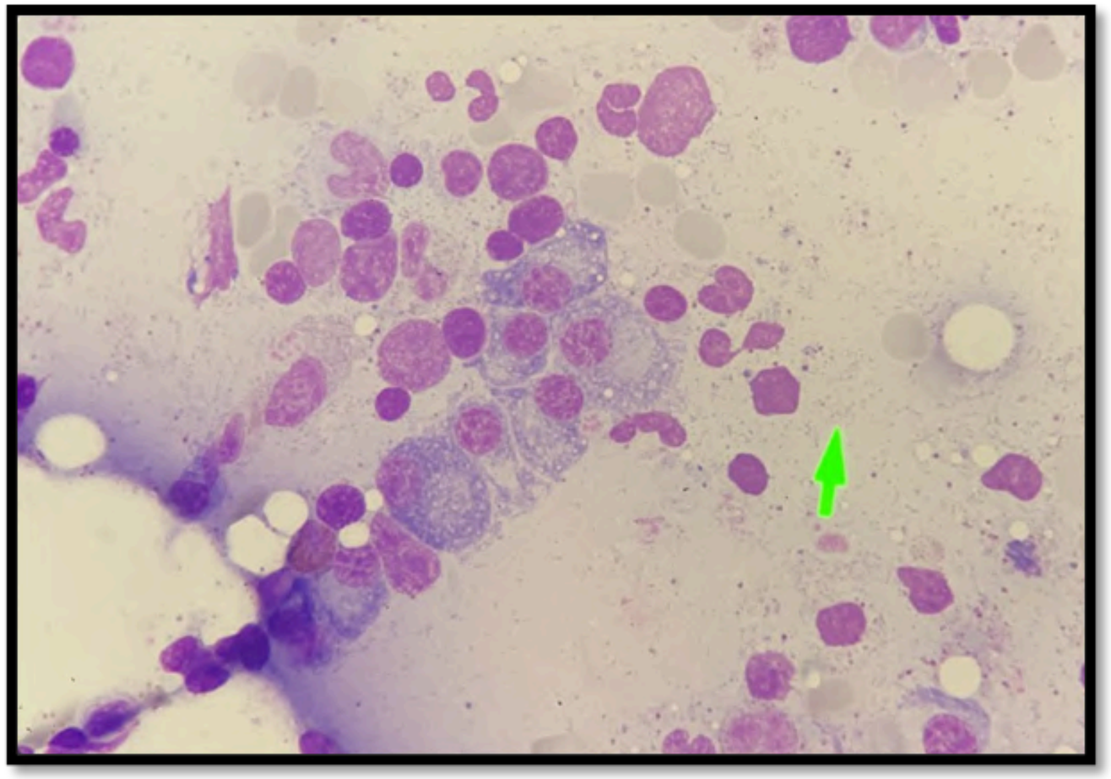
MGUS	Smoldering Myeloma	Active Multiple Myeloma
▪ M-protein < 3 g/dL ▪ Clonal plasma cells in BM < 10% ▪ No myeloma-defining events	▪ M-protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine) ▪ Clonal plasma cells in BM ≥ 10% to 60% ▪ No myeloma-defining events	▪ Underlying plasma cell proliferative disorder ▪ AND ≥ 1 SLiM-CRAB* feature

*S: ≥ 60% clonal bone marrow plasma cells
Li: Serum free light chain ratio ≥ 100 (involved kappa) or ≤ 0.01 (involved lambda)
M: MRI studies with > 1 focal lesion (> 5 mm in size)

C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
R: Renal insufficiency (CrCl < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET/CT)

Multiple myeloma

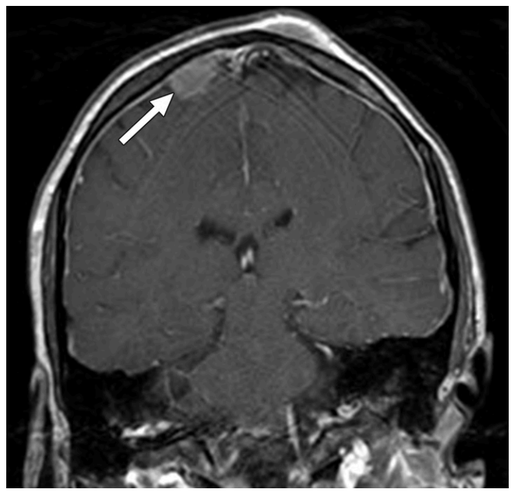




Multiple myeloma

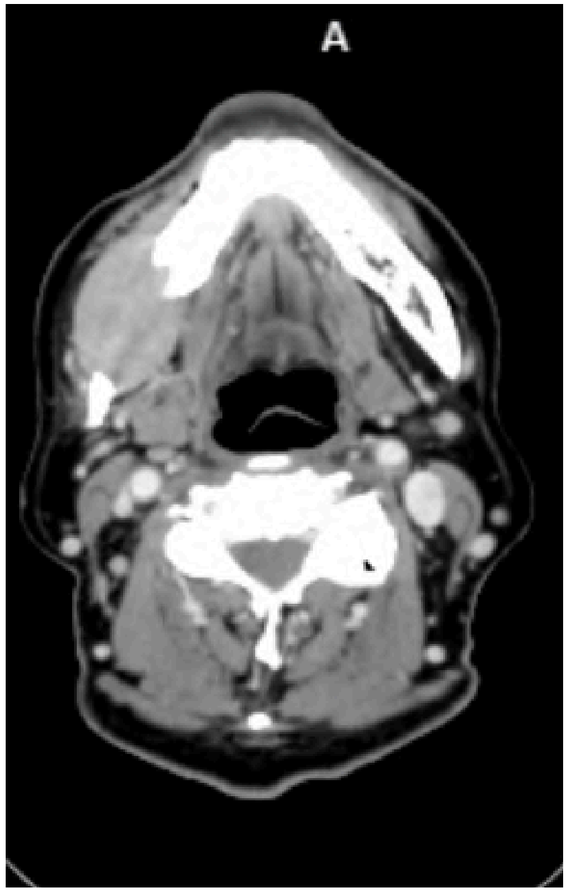
Clinical features

- **Anemia** - fatigue, shortness of breath
- **Skeletal-related events (80%)**
  - bone pain, pathological fractures, spinal cord compression
- **Acute kidney injury (40%)** - nausea, confusion, oliguria
- **Hypercalcemia** - constipation, confusion
- **Recurrent infections**
- **Extramedullary disease (<5%)**
  - skin and soft tissue
- **Bleeding** - BM failure, paraproteinemia
- **Hyperviscosity syndrome** (not common)



AJR Am J Roentgenol. 2010 Nov;195(5):1057-65

Multiple myeloma



Osteolytic lesion form other diseases

Metastatic squamous cell cancer

“Brown tumor” Hyperparathyroidism

Langerhans cell histiocytosis

Tumors and Tumor-Like Lesions of Bone. Springer, Cham.

Multiple myeloma

Definite management

- Anti-myeloma therapies (Daratumumab/Bortezomib-based regimen)
- Transplant eligible or ineligible

Emergency management

- Hypercalcemia - IV hydration, calcitonin, bisphosphonate, steroid
- Cord compression - steroid, RT(EMD), surgery(spinal instability)

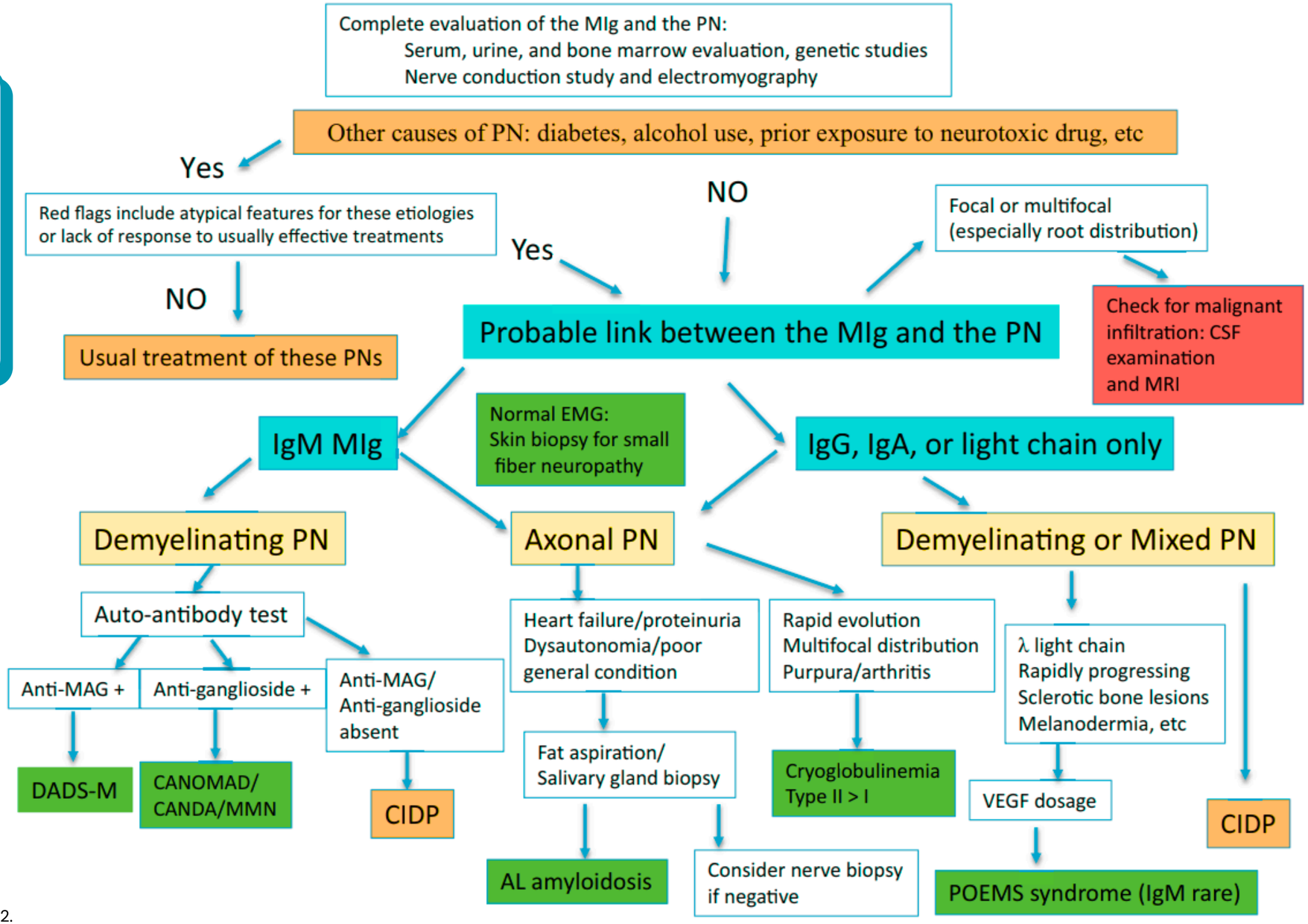
Symptomatic management

- Hypercalcemia - IV hydration, calcitonin, bisphosphonate, steroid
- Renal failure - IV hydration, avoid nephrotoxic drugs, HCO dialysis
- Anemia - blood transfusion, ESAs
- Bone lesions - bone modifying agents (bisphosphonate)

Monoclonal gammopathy–associated peripheral neuropathy

- Atypical CIDP variants
- CIDP with lack of response to treatments
- Systemic symptoms

Immunofixation and SPEP is recommended for all patients suspected CIDP



Hematology Am Soc Hematol Educ Program. 2025 Dec 5;2025(1):385-392.

Monoclonal gammopathy–associated peripheral neuropathy

Feature	POEMS	Cryoglobulinemia	AL amyloidosis
Immunoglobulin type	Almost always λ light chain (IgA > IgG)	Mostly IgM (type II), IgG/IgM type I	70% λ light chain, 50% no intact immunoglobulin
Clinical phenotype	Severe, sensorimotor, often with early pain and weakness	Mixed sensorimotor, painful, distal, and vasculitic	Length-dependent, painful, often with autonomic symptoms
Electrophysiology	Mixed (demyelinating±axonal)	Axonal (mononeuritis multiplex or polyneuropathy)	Axonal, sometimes mixed
Response to IVIG	Poor	Poor	Poor
Clonal targeted therapy	Anti–plasma cell treatment: IMiDs, anti-CD38, ASCT	Rituximab or anti-CD38 based depending on associated proliferation (+ antivirals if HCV)	Anti–plasma cell treatment: PI, anti-CD38, bispecific anti-BCMA
Other key features	Multisystemic, VEGF elevated, sclerotic bone lesions	Systemic symptoms: purpura, arthralgia, glomerulonephritis	Cardiac, renal, autonomic involvement; high NT-proBNP
Prognosis	Severe neurologic sequelae common	Variable, depends on vasculitis severity	Vital prognosis depending on cardiac stage at diagnosis Slow neurologic recovery if hematologic CR

Hematology Am Soc Hematol Educ Program. 2025 Dec 5;2025(1):385-392.

Monoclonal gammopathy–associated peripheral neuropathy

Feature	DADS-M	CANOMAD	CIDP
Onset	Typically >50 years	Middle-aged to older adults	Any age, typically middle-aged
Clinical presentation	Distal symmetric neuropathy, slowly progressive, ataxia, tremor	Chronic sensory ataxia, ophthalmoplegia, bulbar signs, mild weakness	Symmetric motor and sensory symptoms, both proximal and distal
Sensory involvement	Prominent	Prominent	Common
Motor involvement	Mild or moderate, distal	Present but less marked than sensory	Prominent
Cranial nerve involvement	Rare	Frequent (ophthalmoplegia, dysarthria, dysphagia)	Occasional
Monoclonal immunoglobulin association	Strongly associated with IgM (often anti-MAG)	Always associated with IgM (anti-disialosyl gangliosides)	Rare
Autoantibodies	Anti-MAG (IgM)	Anti-GD1b, GD3, GT1b, GQ1b IgM	MIg mainly coincidental
Electrophysiology	Demyelinating, with prolonged distal latencies	Mixed demyelinating and axonal features	Demyelination with temporal dispersion
Response to IVIg	Poor	Partial or transient	Often good
Response to rituximab	Often beneficial in anti-MAG+ cases	Often beneficial	Variable
Prognosis	Slowly progressive, limited recovery	Fluctuating course, chronic	Variable; many improve with treatment

Hematology Am Soc Hematol Educ Program. 2025 Dec 5;2025(1):385-392.

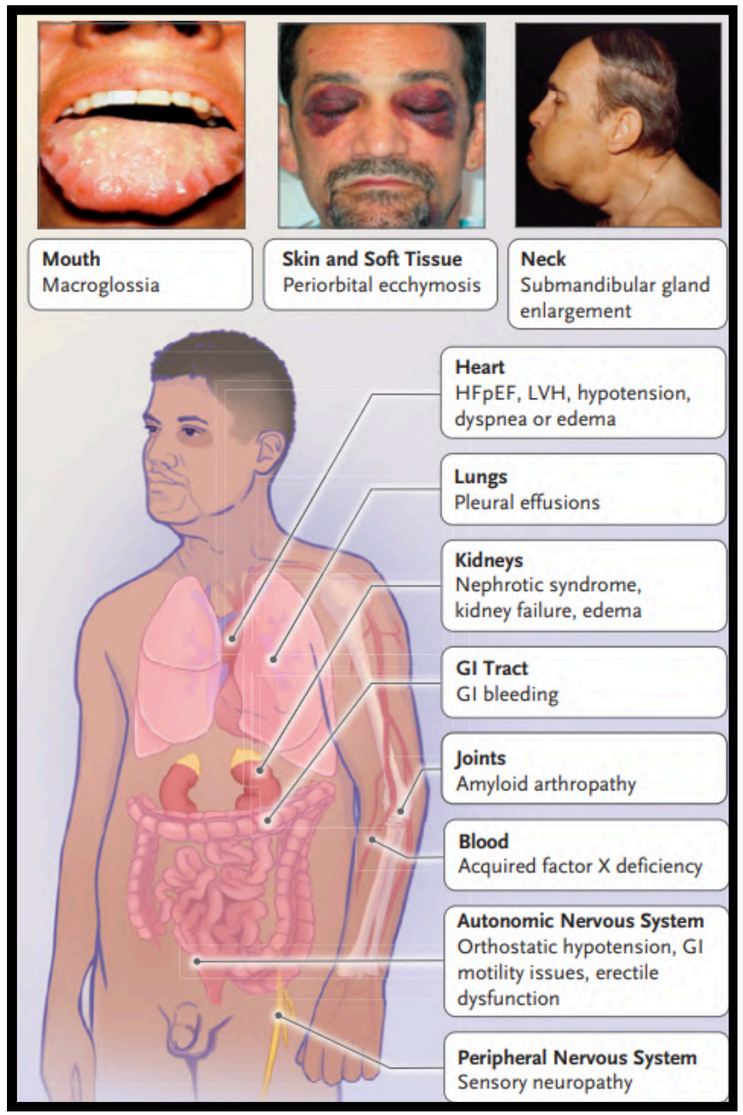
Amyloidosis

- A heterogeneous disease that results from the deposition of toxic insoluble beta-sheet fibrillar protein aggregates in different tissues

Amyloid type	Precursor protein	Major organ involvement					
		Heart (bone tracer uptake)*	Kidney	Liver	PNS	ANS	ST
AL amyloidosis (acquired)	Immunoglobulin light chain	+++ (usually absent, can be intense)	+++	++	+	+	++
ATTRv amyloidosis (hereditary)	Mutated transthyretin	+++ (usually intense, can be absent in some variants)	—	—	+++	+++	—
ATTRwt amyloidosis (acquired)	Wild-type transthyretin	+++ (usually intense)	—	—	—	—	+
ApoAI amyloidosis (hereditary)	Mutated apolipoprotein AI	+ (present)	+	+++	—	—	—
AA amyloidosis (acquired)	Serum amyloid A protein	+	+++	+	—	+	—
ALECT2 (acquired)	Leukocyte chemotactic factor 2	—	+++	+	—	—	—

Blood (2020) 136 (23): 2620–2627.

Clinical manifestation



Skin and soft tissue (AL amyloidosis)
- macroglossia, skin lesion, CTS (ATTR)

Cardiac (50% of AL amyloidosis)
- HFpEF, Rt sided HF (edema), low voltage EKG, hypotension, arrhythmia, LVH

Kidney (AL, AA amyloidosis)
- nephrotic syndrome, renal failure (advance)

GI tract
- bowel habit change, hypoalbuminemia, GIB
- pseudo-obstruction, delay gastric emptying

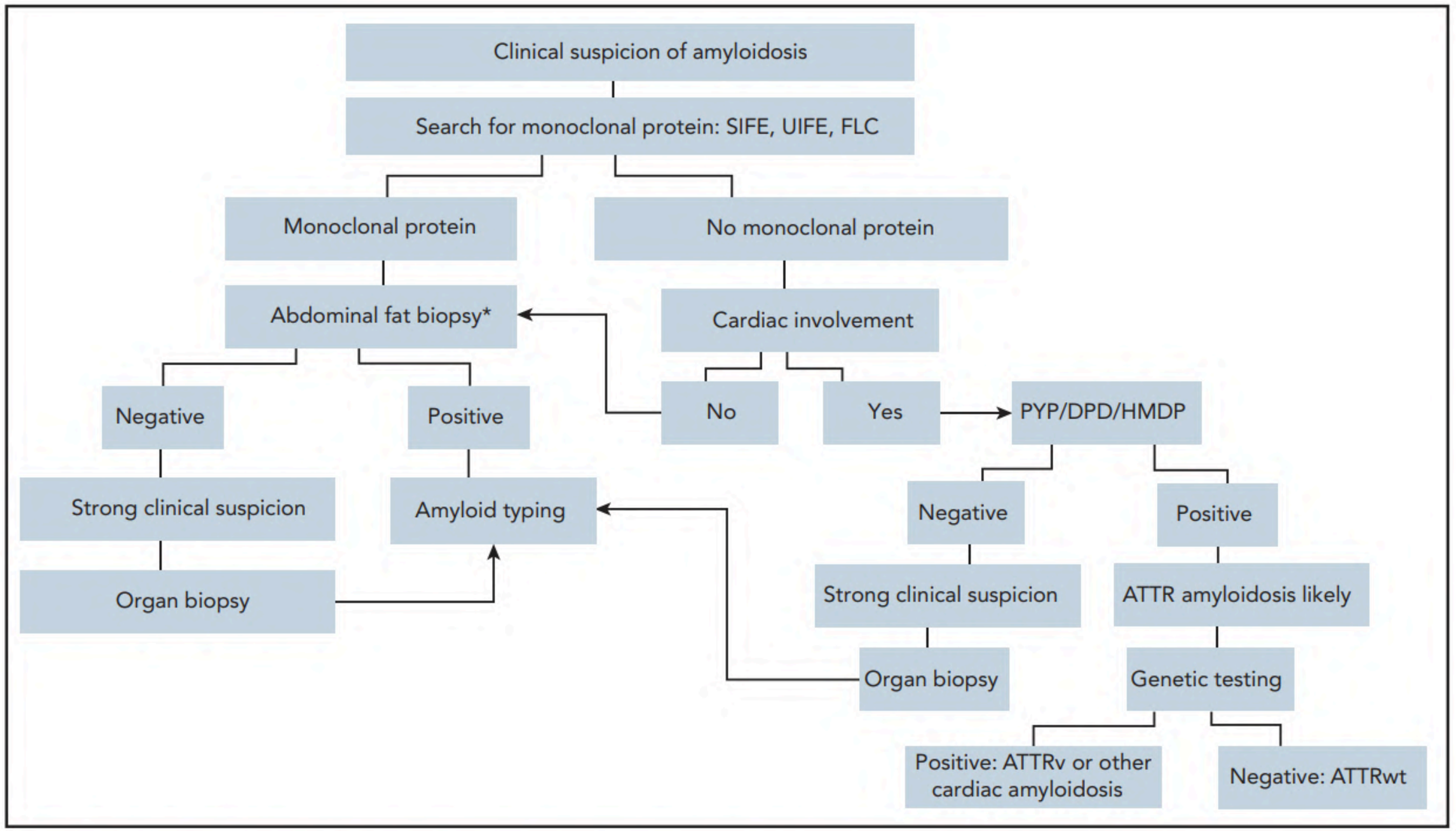
Liver and spleen
- hepatomegaly (w/o HF), ALP elevation (>1.5x)
- early satiety, splenomegaly

PNS and ANS (AL amyloidosis)
- peripheral neuropathy, postural hypotension

Lung
- pleural effusion, diffuse interstitial lung

n engl j med 390;24

Investigation of amyloidosis



Blood. 2022;139(19):2918-2930

Treatment of amyloidosis

- **Decrease amyloid protein**
  - AA : control infection/inflammation
  - ATTR : Stabilizer(Tafamidis), Silencer(Patisiran, Inotersen), Liver transplant
  - AL : CMT(VCD, Dara-VCD), ASCT
- **Increase amyloid fibril degradation**
- **Organ transplant**
  - AA : kidney transplant
  - ATTR : heart transplant
  - AL : kidney, heart transplant

POEMS syndrome

- Rare paraneoplastic syndrome due to underlying plasma cell disorder
- Median age 50-60 years

Polyneuropathy

Organomegaly

Endocrinopathy

Monoclonal Gammopathy

Skin Changes

Papilledema

Extravascular volume overload

Sclerotic bone lesions

Thrombocytosis/polycythemia

TABLE 1 Criteria for the diagnosis of POEMS syndrome[a]

Mandatory major criteria	1. Polyneuropathy (typically demyelinating)
	2. Monoclonal plasma cell-proliferative disorder (almost always λ)
Other major criteria (one required)	3. Castleman disease[a]
	4. Sclerotic bone lesions
	5. Vascular endothelial growth factor elevation
Minor criteria	6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
	7. Extravascular volume overload (edema, pleural effusion, or ascites)
	8. Endocrinopathy (adrenal, thyroid,[b] pituitary, gonadal, parathyroid, pancreatic[b])
	9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)
	10. Papilledema
	11. Thrombocytosis/polycythemia[c]
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B_{12} values

Am J Hematol. 2019;94:812–827.

Clinical features of POEMS syndrome

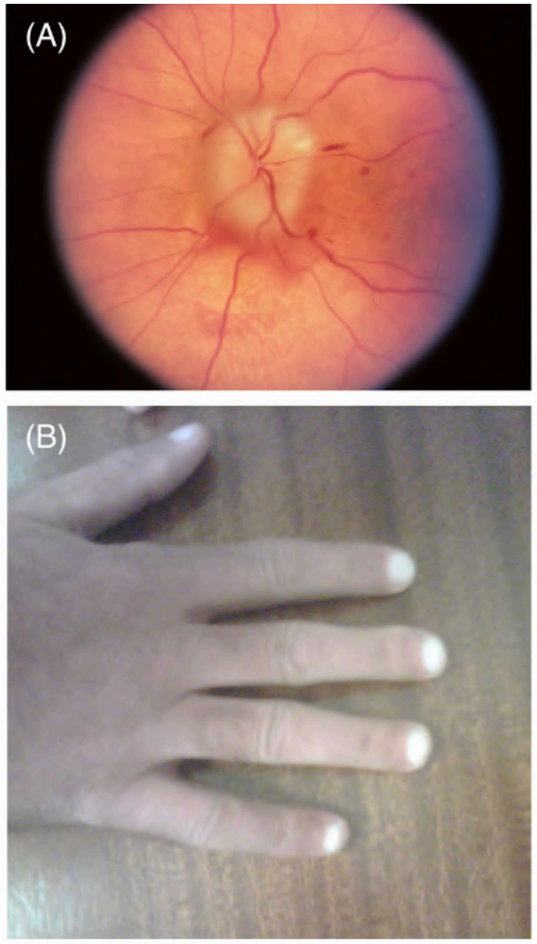
- Subacute, distal, symmetrical, sensorimotor neuropathy that progressively worsens (100%)
  - begin with sensory neuropathy, **lower limbs**
  - **neuropathic pain** is common
- Organomegaly (50%)
  - hepatosplenomegaly, lymphadenopathy
- Sclerotic bone lesions (95%)
- Endocrinopathies (84%) - multiple
  - **hypogonadism** (most common), hypothyroid, DM
- Hyperpigmentation, hemangiomata (50%)
- Papilledema, peripheral edema (30%)
- Effusion - pleural, pericardial, ascite
- Other symptoms and signs
  - Clubbing, weight loss, hyperhidrosis, PHT/restrictive lung disease, arterial thrombosis

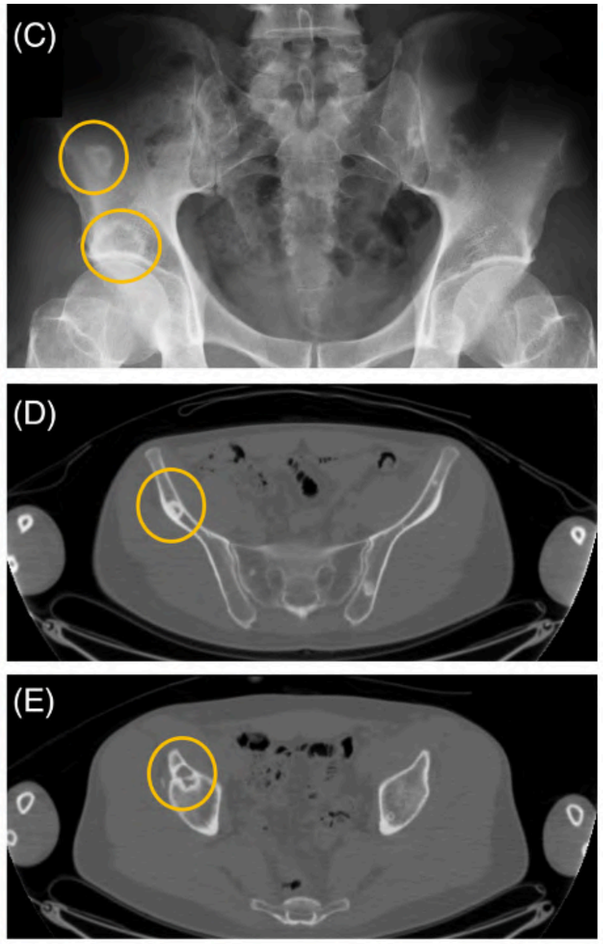
	Characteristic		% with feature	
P	Peripheral neuropathy	★	100	★
O	Organomegaly	★	45-85	
E	Endocrinopathy		67-84	
M	Monoclonal plasma cell disorder	★	100	★
S	Skin changes	★	68-89	
P	Papilledema		29-64	
E	Extravascular volume overload	★	30-90	
S	Sclerotic bone lesions	★	60-96	
T	Thrombocytosis	★	>50	
	High VEGF	Not tested		
	Abnormal PFTs	★		
	Pulmonary hypertension	★	27	

Am J Hematol. 2019;94:812–827.

POEMS syndrome - VEGF mechanism of action

Optic disc edema





Mixed lytic osteosclerotic bone lesions (CT is prefered)

Glomerular hemangiomata

Hypertrichosis

Neurology® 2020;95:1-e12.
Am J Hematol. 2019;94:812–827.

Recommended testing for POEMS syndrome

Investigation from blood

- CBC
- SPEP with SIFE, sFLC, Ig level
- VEGF and IL-6
- Testosterone, estradiol, FBS, TSH, prolactin

Other studies

- Nerve conduction studies
  - a length-dependent sensorimotor neuropathy, typically demyelinating, but with axonal degeneration
- Skeletal CT (bone lesions, organomegaly, effusions)
- BMA, BM biopsy
  - few clonal plasma cells, megakaryocyte hyperplasia
- Echocardiography (RV function and PHT)
- PFT with DLCO (restrictive lung, PHT)
- Urine total protein, UPEP, Urine IFE

TABLE 1 Criteria for the diagnosis of POEMS syndrome[a]

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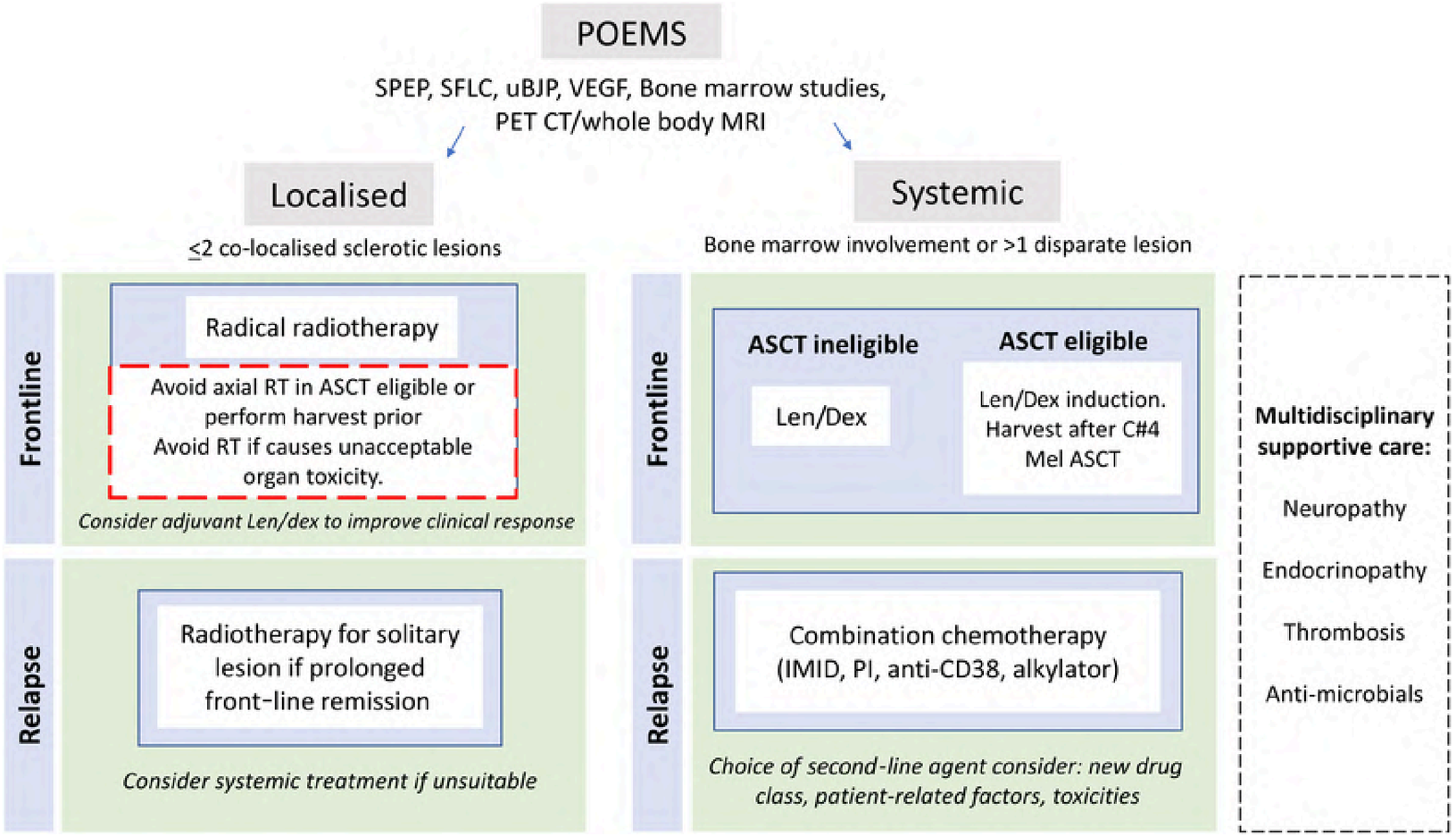
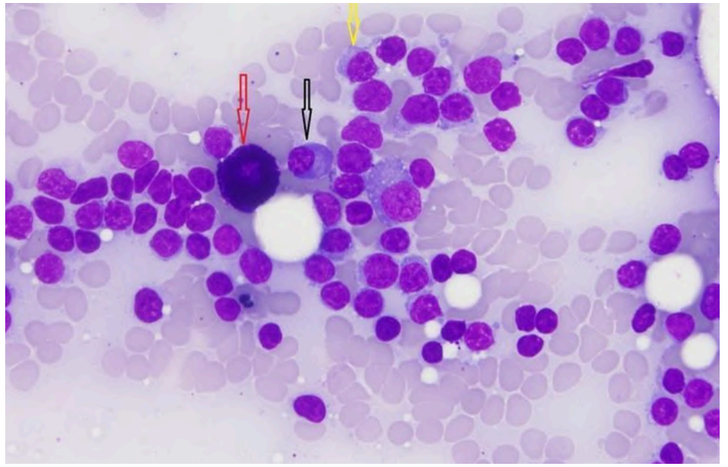
Treatment of POEMS syndrome



Regimen	Outcome
Radiation	50%–70% of patients have significant clinical improvement
Melphalan-dexamethasone	81% hematologic response rate; 100% with some neurologic improvement
Corticosteroids	50% of patients have significant clinical improvement
Cyclophosphamide-dexamethasone	At least 50% of patients have significant improvement
ASCT	100% of surviving patients have significant clinical improvement
Thalidomide-dexamethasone	Reported responses, but not recommended as first line due to risk of neuropathy
Lenalidomide-dexamethasone	75%–95% patients have significant clinical improvement and VEGF improvement
Bortezomib	Nearly 100% in combination with cyclophosphamide and dexamethasone. Caution regarding risk of worsening neuropathy. Usually used after first line.
Bevacizumab	No consistent benefit

Br J Haematol. 2023 Jan;200(2):128-136.
Hematology Am Soc Hematol Educ Program (2025) 2025 (1): 393–400.

Waldenström Macroglobulinaemia



Definition

- **Lymphoplasmacytic lymphoma** with BM involvement
- **IgM** monoclonal gammopathy of any concentration

Clinical features

- Asymptomatic (20-30%)
- Anemia (80%)
- Constitutional symptoms (50-60%)
- Organomegaly, EMD (10-30%)
- Hypercalcemia (4%)

IgM related syndromes

- Cryoglobulinemia (10%) - type I
- Hyperviscosity syndrome (10-15%)
- Peripheral neuropathy (10-20%)
- Cold agglutinin disease (5%) – usually titer >1:1000
- Amyloidosis(5-10%), MIDD

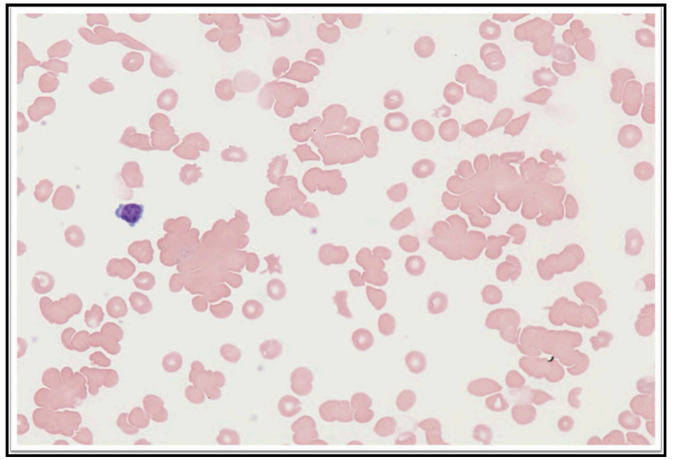
Blood (2016) 127 (20): 2375–2390.

IgM related syndromes

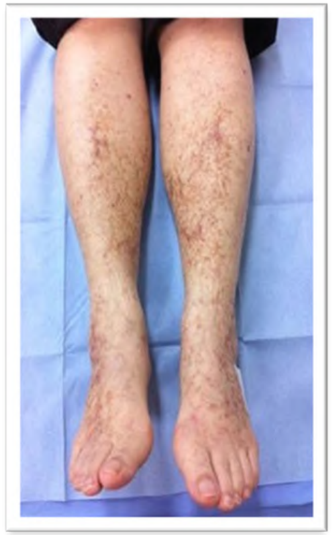
Hyperviscosity syndrome

Headache, dizziness, ataxia,
blurry vision, retinal hemorrhage
encephalopathy, stroke, seizure
mucocutaneous bleeding

CAIHA



Cryoglobulinemia



- Vasculitis, acrocyanosis,
cutaneous ulcers, purpura
- Raynaud's phenomenon,
arthralgias, renal dysfunction

Blood. 2018;132(13):1379-1385
Nature Reviews Disease Primers volume 4, Article number: 11 (201

Treatment of WM

- Watch and wait
- Chemoimmunotherapy
- Proteasome inhibitors
- BTK inhibitors
- Emergency treatment
  - HVS - plasmapheresis
- Stem cell transplantation

Table 4. Indications to start therapy in a patient with a diagnosis of WM

Clinical indications for initiation of therapy
Recurrent fever, night sweats, weight loss, fatigue
Hyperviscosity
Lymphadenopathy: either symptomatic or bulky (≥5 cm in maximum diameter)
Symptomatic hepatomegaly and/or splenomegaly
Symptomatic organomegaly and/or organ or tissue infiltration
Peripheral neuropathy because of WM
Laboratory indications for initiation of therapy
Symptomatic cryoglobulinemia
Symptomatic cold agglutinin anemia
Autoimmune hemolytic anemia and/or thrombocytopenia
Nephropathy that is related to WM
Amyloidosis that is related to WM
Hemoglobin ≤10 g/dL
Platelet count <100 × 10^9/L

Blood (2016) 127 (20): 2375–2390.

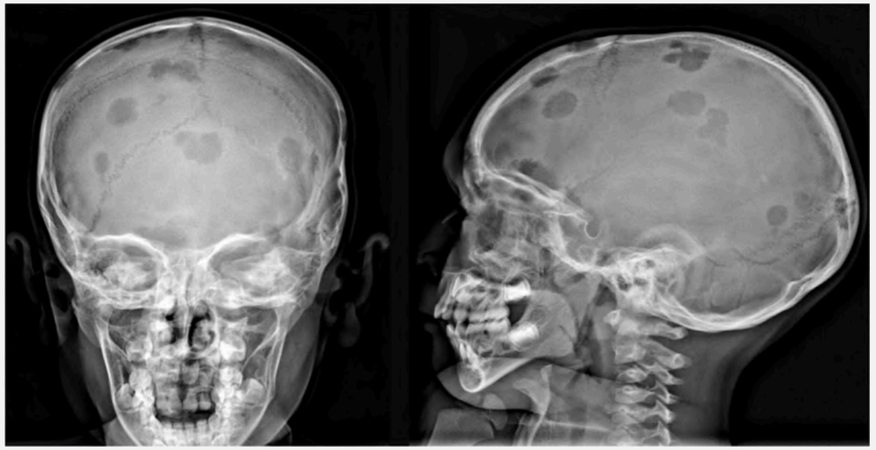
Case

Case 1: Hypopituitarism

Patient: Female, 22-year-old

Presentation: polyuria, secondary amenorrhea for 1 year

Clinical Focus: pituitary lesion



Case 2: Cystic lung disease

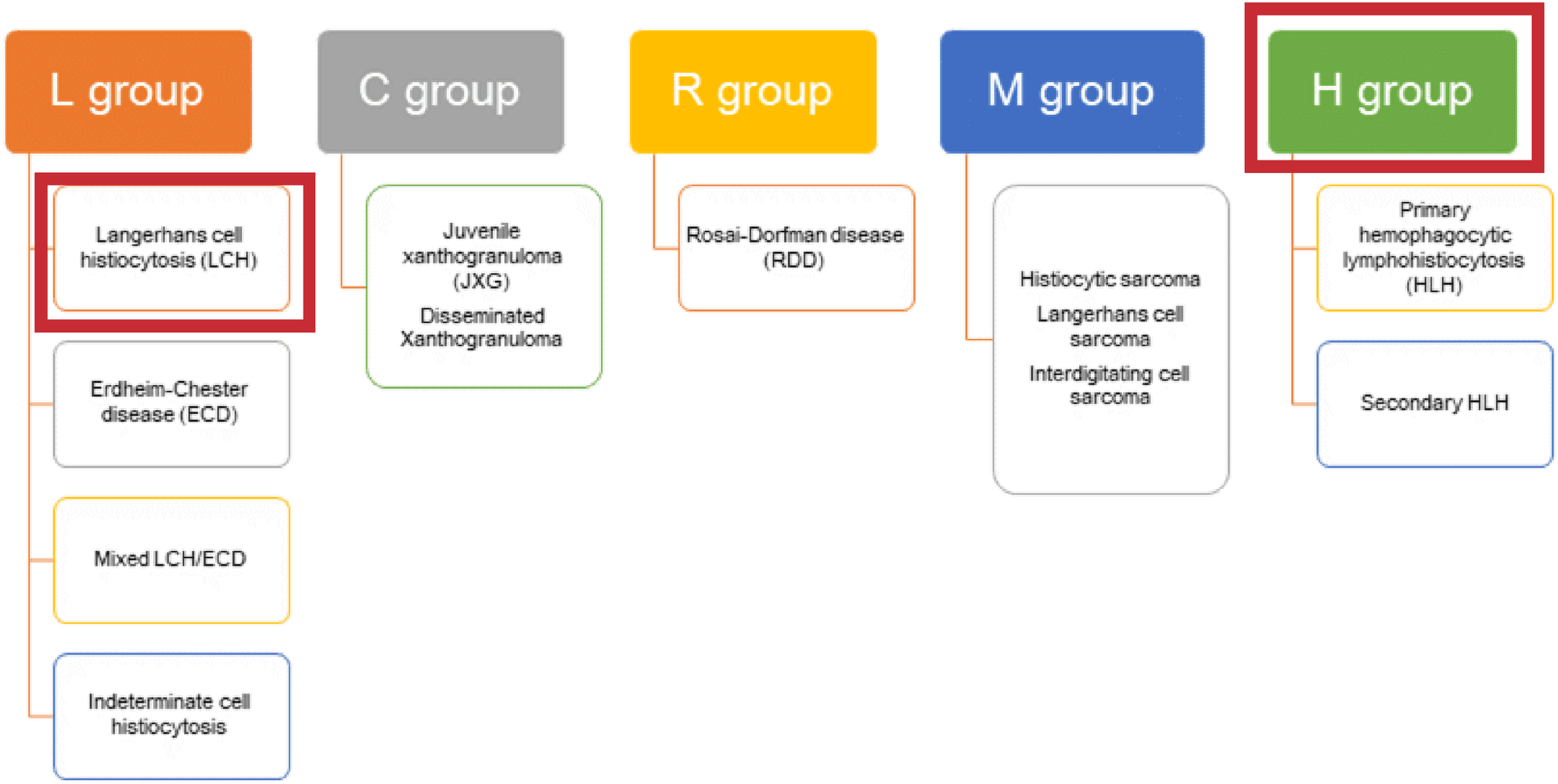
Patient: Male 30-year-old

Presentation: acute dyspnea for 2 days

Clinical Focus: Pneumothorax

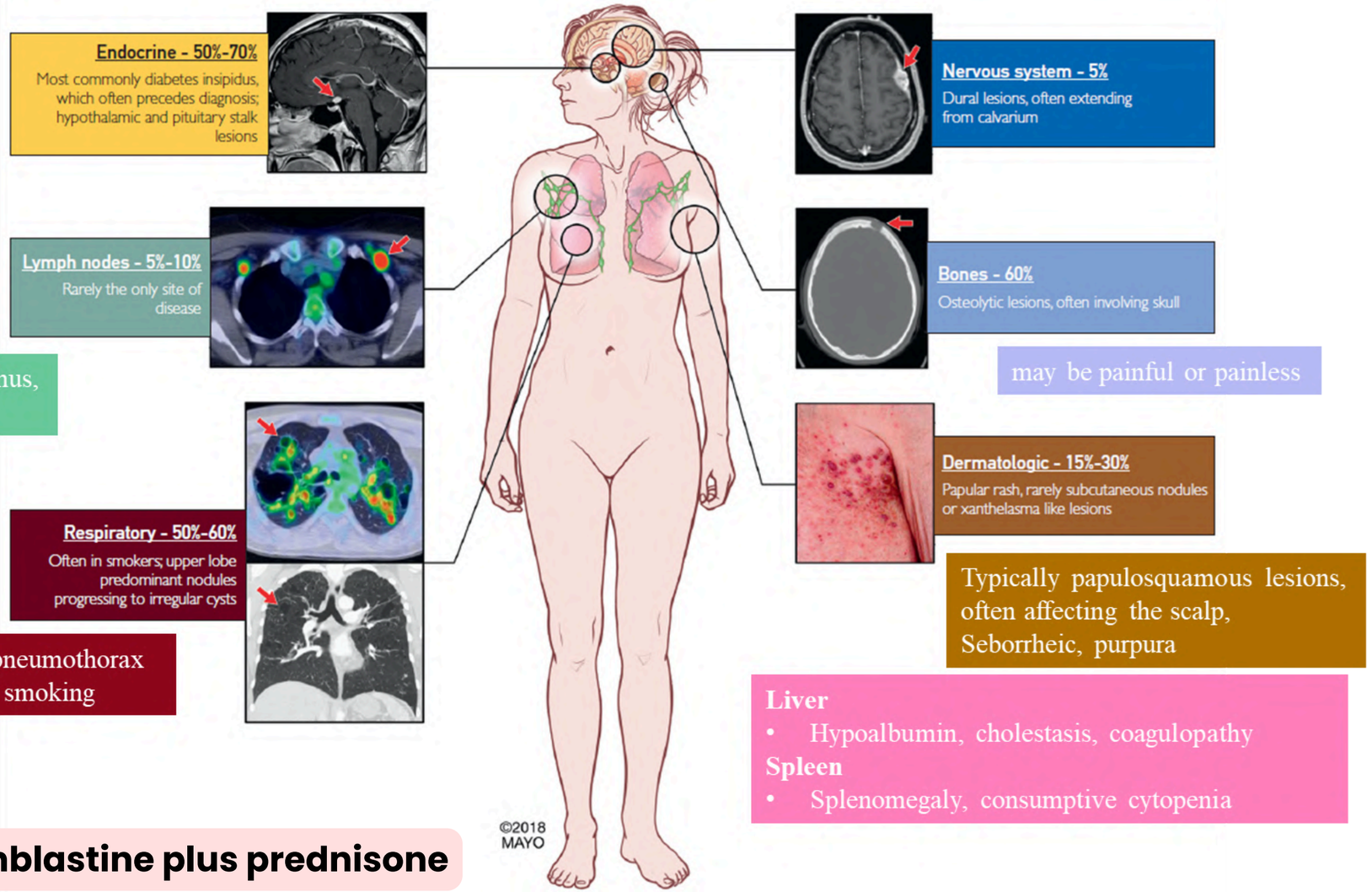
- Chronic cough for 3 months
- History of smoking

Histiocytic disorders



Mayo Clin Proc. 2019;94(10):2054-2071

Langerhans cell histiocytosis



Cervical node, thymus, mediastinal node

- Spontaneous pneumothorax
- Associated w/ smoking

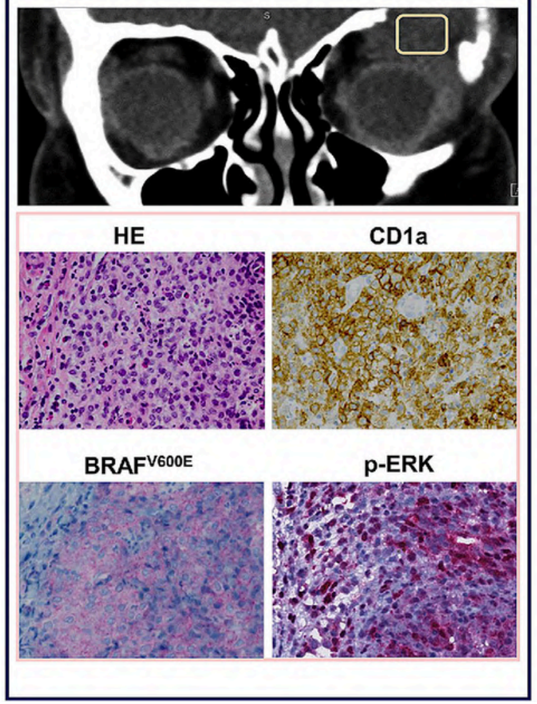
may be painful or painless

Typically papulosquamous lesions, often affecting the scalp, Seborrheic, purpura

Liver
- Hypoalbumin, cholestasis, coagulopathy

Spleen
- Splenomegaly, consumptive cytopenia

histopathology

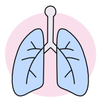


Vinblastine plus prednisone

Mayo Clin Proc. 2019;94(10):2054-2071

Histiocytosis







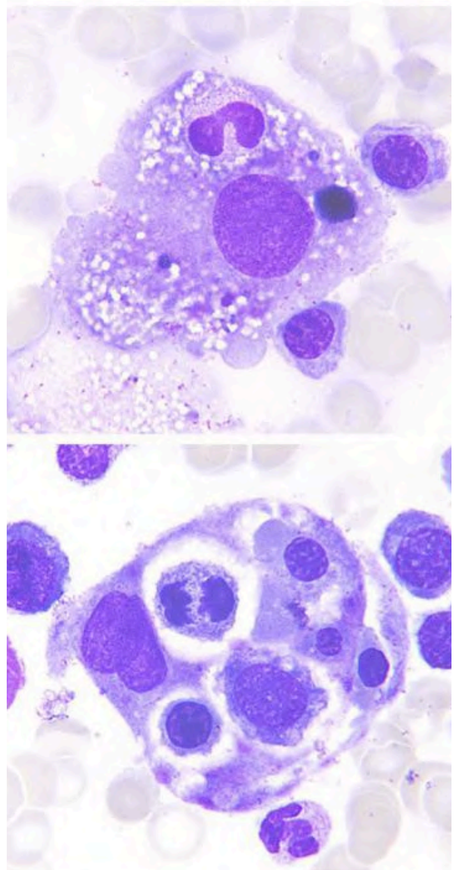

Feature	Erdheim-Chester Disease (ECD)	Langerhans Cell Histiocytosis (LCH)	Rosai-Dorfman Disease (RDD)
Bones	95% osteosclerosis at long bones	60% osteolytic lesions often skull	less common
Endocrine	Diabetes Insipidus (DI) - common	Diabetes Insipidus (DI) - common	
Respiratory	50% mediastinal infiltration, pleural/septal thickening	50%–60% ; mostly in smokers; nodules in early stages and cysts in later stages.	10%–20% involves large airways and sinuses
Dermatologic	25% xanthelasma-like lesions	15%–30% papular rash	50% subcutaneous nodules
Arterial	50%–80% periaortic infiltration ("coated aorta")		less common
Retroperitoneum	40%–50% frequency; perinephric infiltration ("hairy kidneys")		5%–10% hilar masses, subcapsular infiltration
Lymph Nodes			30%–50% isolated or generalized LN
Orbits	30% orbital masses.		

Mayo Clin Proc. 2019;94(10):2054-2071

Hemophagocytic lymphohistiocytosis (HLH)

Clinical - persistent fever, hepatosplenomegaly, cytopenia, liver dysfunction, sepsis like

HLH-2024[12] (5 of 7 criteria)[a]	HScore[c,13]
	Known underlying immunodepression
1) Fever	<38.4 °C (101.12 °F) 38.4–39.4 °C (101.12–102.92 °F) >39.4 °C (102.92 °F)
2) Splenomegaly	Splenomegaly Hepatomegaly
3) Cytopenia in ≥2 of 3 cell lines • Hemoglobin <90 g/L • Platelets <100×10⁹/L • Neutrophils <1.0×10⁹/L	Hemoglobin ≤/≥9.2 g/dL (5.71 mmol/L) Leukocytes ≤/>5000 mm³ Platelets ≤/>110000 mm³
4) Hypertriglyceridemia and/or hypofibrinogenemia • Fasting triglycerides ≥3 mmol/L • Fibrinogen ≤1.5 g/L	Higher triglycerides (mmol/L) <1.5; 1.5–4; >4 Lower fibrinogen <2.5 g/L; >2.5 g/L Higher GOT/ASAT (IU/L) <30, ≥30
5) Hemophagocytosis in spleen/bone marrow/ lymph node • No evidence of malignancy	Hemophagocytosis in bone marrow
6) Ferritin ≥500 µg/L	Ferritin <2000 ng/mL 2000–6000 ng/mL >6000 ng/mL
7) Soluble CD25 ≥2400 U/mL	



Primary HLH(pediatric or young adult)

- Defects in the cytolytic function of cytotoxic T cells and/or NK cells

Secondary HLH (typical in Adult)

- Infections (mainly viruses, such as **EBV**, HIV, and CMV, but also bacteria, parasites, and fungi)
- Malignancies (mainly **malignant lymphoma**)
- MAS in autoinflammatory or autoimmune (**SLE**, AOSD)
- Other causes

Blood (2019) 133 (23): 2465–2477.

Hemophagocytic lymphohistiocytosis (HLH)

Primary HLH	HLH-94 (Etoposide, cyclosporin A, steroid)
Infection associated HLH	Steroid (+/-IVIG), antimicrobial agents
Malignancy associated HLH	Steroid(+/-IVIG), Etoposide (”pre-phase”), chemotherapy (disease adapted)
MAS-HLH	High dose methylprednisolone, CSA, anakinra, (disease adapted)

Blood (2019) 133 (23): 2465–2477.

Thank you for your attention

&

Good luck EXAM!