Common problems in Hematology

Parivat Thitiarayavich, MD

Division of Hematology, Department of Medicine

Faculty of Medicine, Thammasat University

Long case examination

Approach

Clinical findings

DDx

Diagnosis & Management

Hematological disease

Common

- Lymphoma(HL, B-NHL)
- Myeloproliferative neoplasm
- MM/amyloidosis
- Acute leukemia
- Thalassemia
- AIHA, G-6PD deficiency
- Nutritional deficiency anemia
- Thrombophilia, APS

Rare

- Lymphoma(T-cell NHL)
- Langerhans cell histiocytosis
- IgG-4 related disease
- POEMS
- Eosinophilic syndrome
- TTP, acquired hemophilia A
- Osler Weber Rendu
- HS, SAO, PNH
- PRCA

Common hematological symptoms

- Anemia
- Pancytopenia
- Bleeding
- Lymphadenopathy
- Splenomegaly
- Thrombosis

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

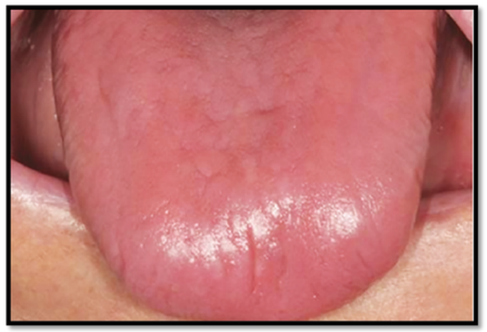
Clinical approach to cytopenia

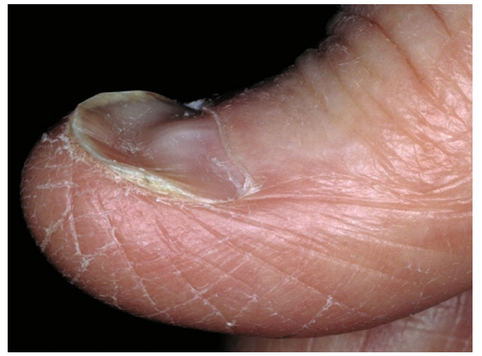
- **Splenomegaly** – infection, NHL, PMF, autoimmune, ALL, AML M4/5, HLH
- **Massive splenomegaly** – Overt PMF, splenic lymphoma, CML blastic
- **Lymphadenopathy** – lymphoma, Infections, ALL, AML M4/5, cancer
- **Neurological deficit** – Vitamin B 12 deficiency, paraneoplastic
- **History of gastric surgery** – Megaloblastic anemia, copper deficiency
- **Dark urine** – PNH (splanchnic thrombosis, CVST)
- **Significant weight loss** – malignancy, chronic infection(disseminated TB)
- **Bone pain** - multiple myeloma, bone metastasis

Nutritional anemia

Iron deficiency anemia

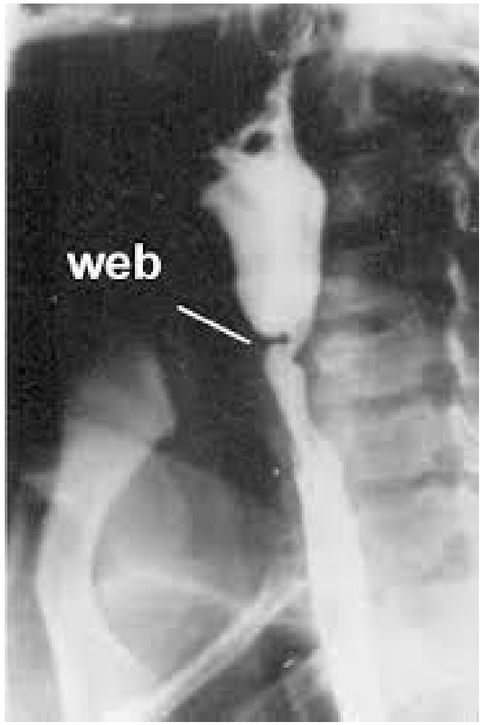
- S&S : fatigue, DOE, pica, pagophagia, glossitis, cheilosis, koilonychia





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)

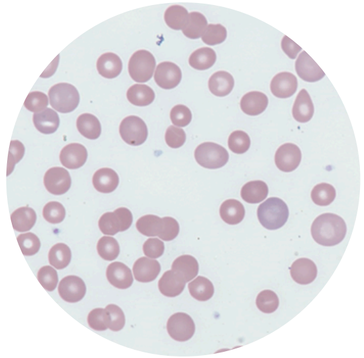


Plummer-Vinson syndrome

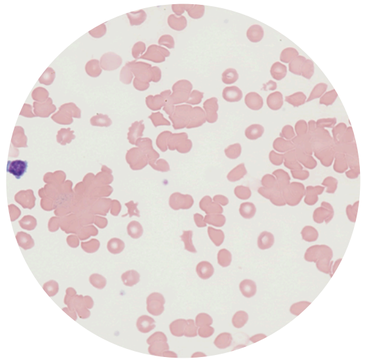
- Iron-deficiency anemia
- Esophageal webs
- Dysphagia (intermittent)

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

Acquired Hemolytic anemia



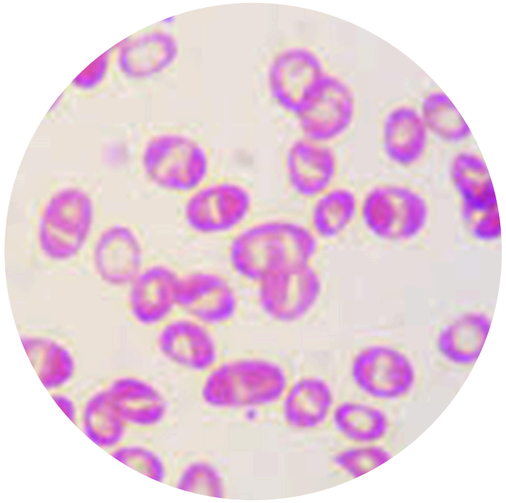
- **WAIHA** DCT + Treat cause + Corticosteroid
  - acute or chronic, extravascular hemolysis, **splenomegaly**
  - secondary: SLE, CLL or indolent lymphoma, AITL



- **CAIHA** DCT + Treat cause + Keep warm
  - chronic, mild anemia, **acrocyanosis, Raynaud,** thrombosis
  - secondary: LPD, mycoplasma, EBV
- **PNH** DCT - Flow for CD 55/59 Eculizumab
  - **intravascular hemolysis**: jaundice, dark urine
  - pancytopenia, (IDA due to chronic hemolysis)
  - thrombosis : **cerebral veins , intraabdominal veins** (Budd-Chiari syndrome)

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**

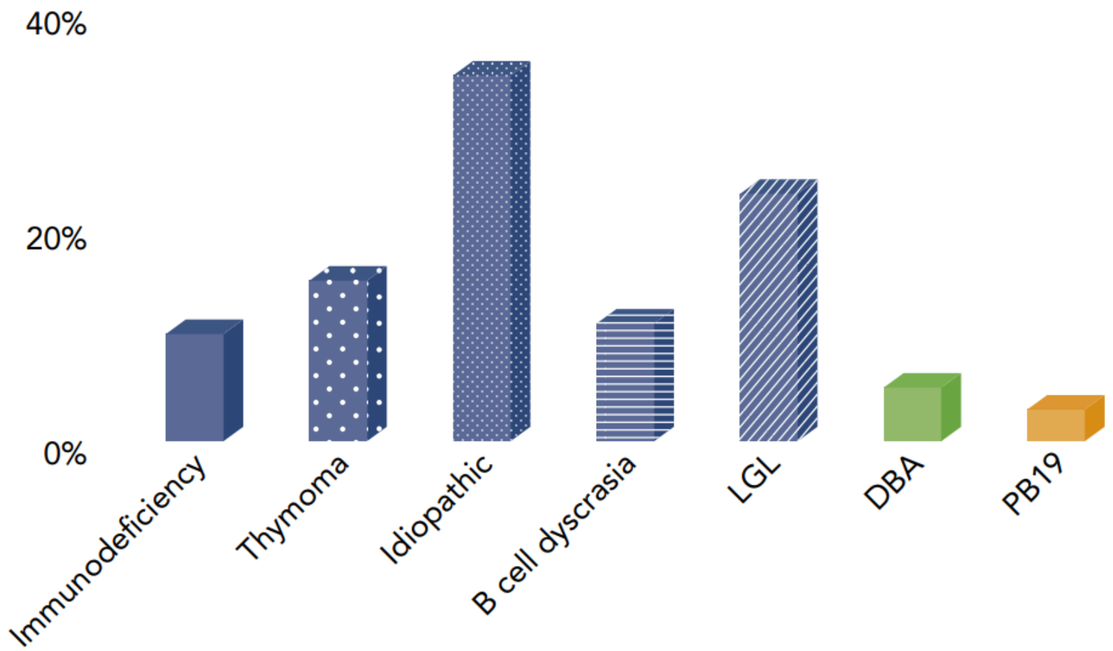
Pure red cell aplasia

Definition

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

Diagnostic criteria

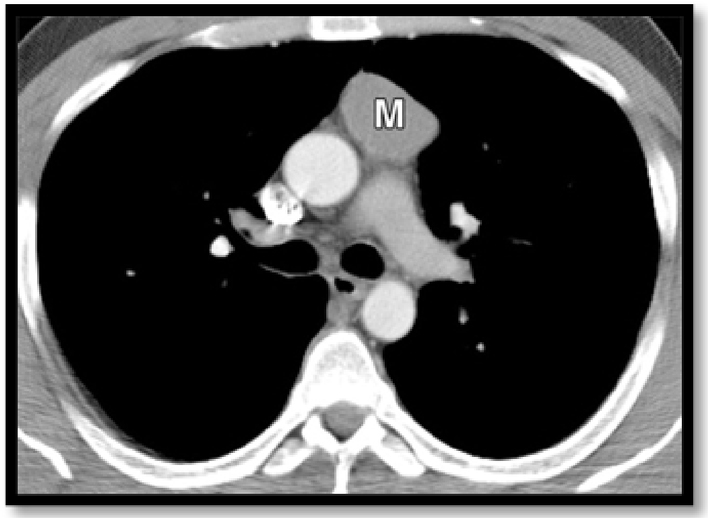
- Fall in RBC 1% per day
- Reticulocyte count <1% or <10,000
- No major change in WBC, platelet
- Normal cellularity of BM with normal myeloid cells and megakaryocytes
- < 1% of erythroblasts (or < 5%)



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

Pure red cell aplasia

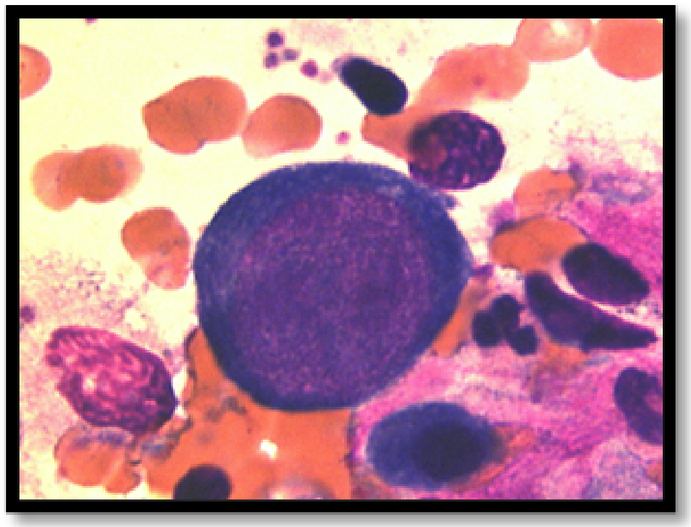
Thymoma



Management

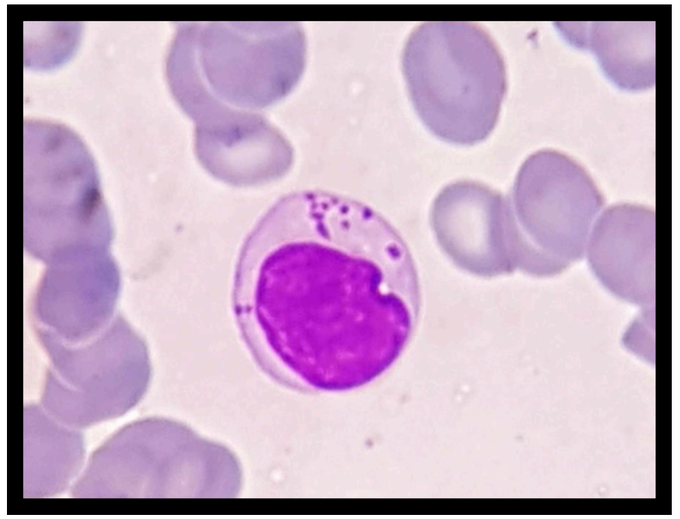
- Thymectomy
- Steroid + IST

Parvo B19



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

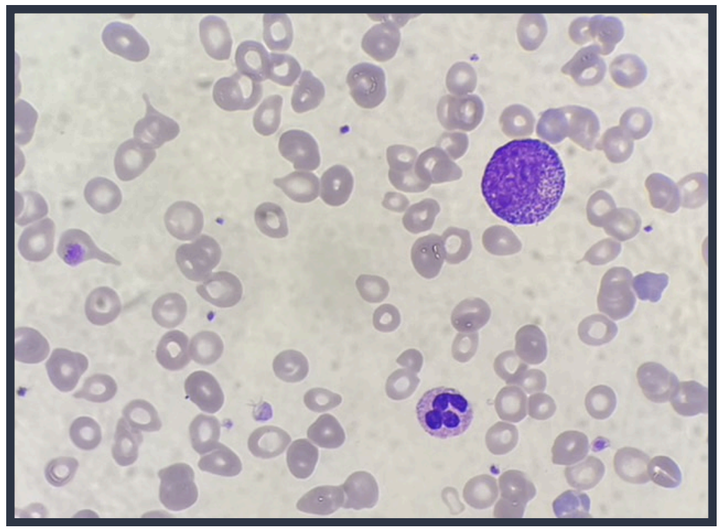
LGL leukemia

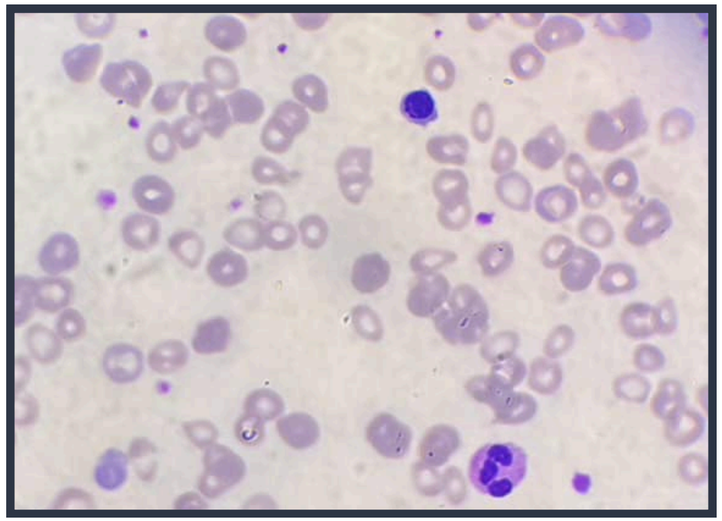


- Associated with autoimmune disease
- Neutropenia
- Splenomegaly
- Flow cytometry
- Oral Cy + Prednisolone

Myelophthisic anemia

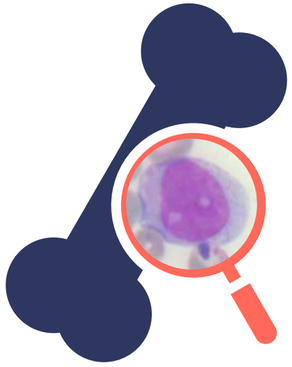
- **Metastatic solid malignancy (prostate, lung, breast)**
- **Myelofibrosis**
- Hematologic malignancy (MM, lymphoma, leukemia)
- Infection (fungal infections and tuberculosis)
- Gaucher disease
- Sarcoidosis



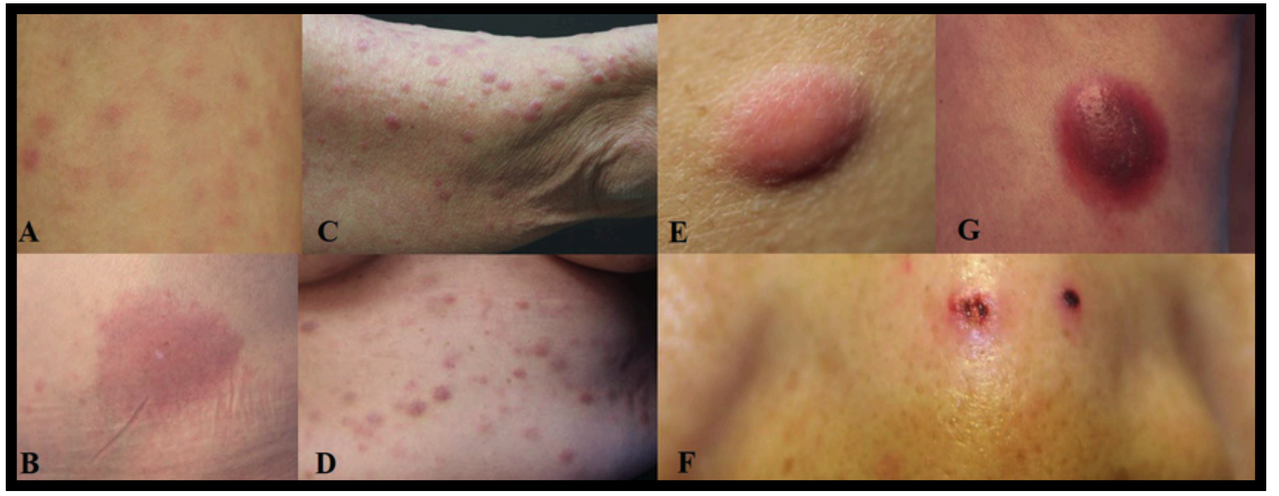


Acute leukemia

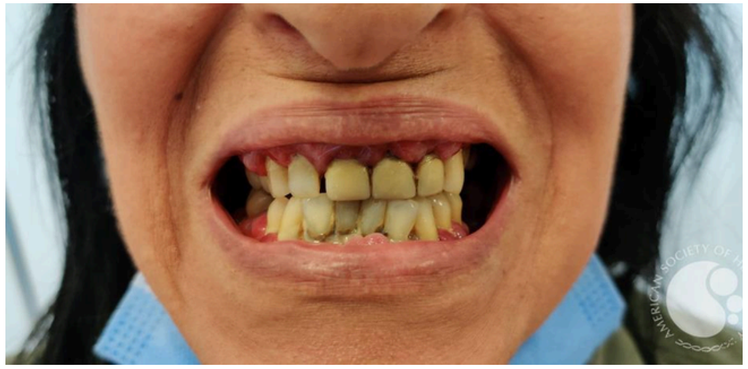
Acute to subacute bone marrow failure



Leukemic cutis (AML M4/5)



Gum hypertrophy (AML M4/5)



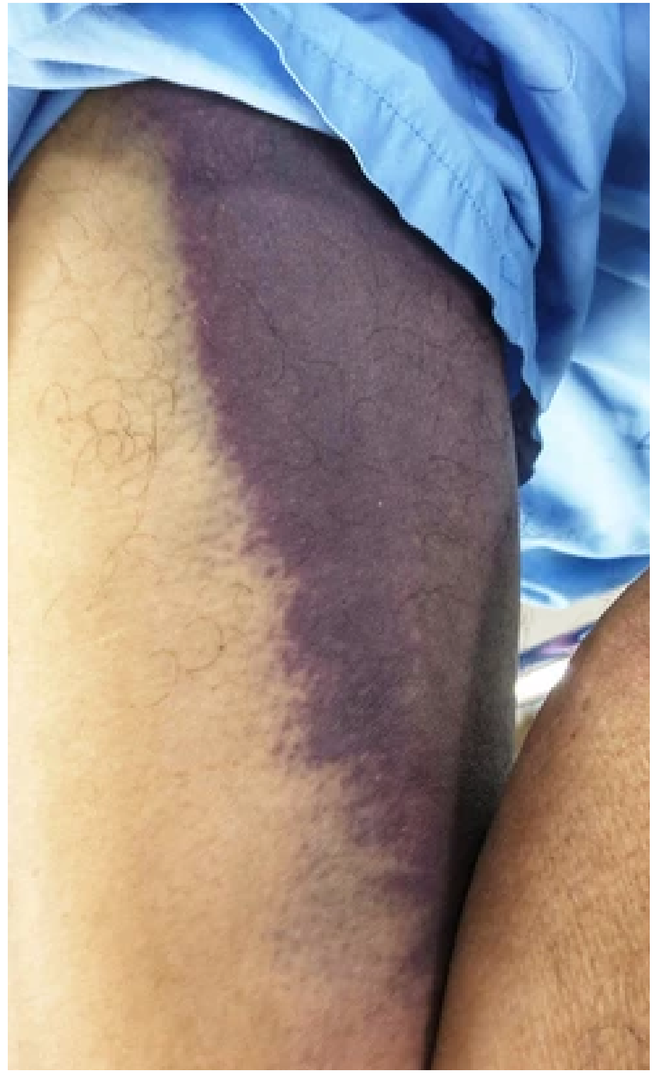
Acute lymphoblastic leukemia

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

Acta Derm Venereol. 2022;102:adv00647.

Case

- Female 76-year-old
- U/D T2DM
- Presented with abnormal bleeding for 1 mo
- No history of fever, weight loss
- No history of Herbal use
- PE: as shown in the figure



Approach to bleeding disorder

- **Local *vs* Systemic bleeding**

  - Spontaneous bleeding
  - Multiple site bleeding
  - Inappropriate bleeding to injury

  - Prolonged bleeding
  - Family history of bleeding disorder
  - Drug use
  - Underlying disease

	Primary	Secondary
Onset	Immediate	Delay
Site	Superficial ecchymosis Petechiae Mucosal bleeding Menorrhagia	Deep ecchymosis Hematoma Hemarthrosis Intramuscular

- **Primary vs Secondary**

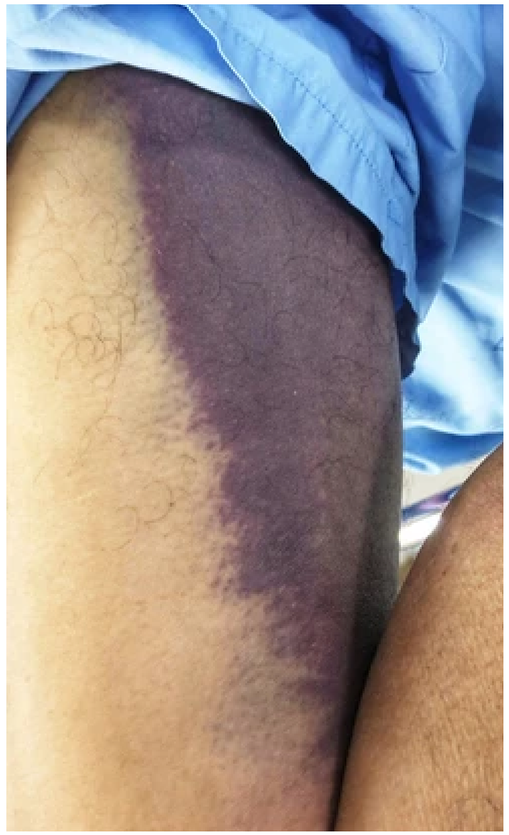
  - Blood vessel
  - Platelet
  - vWF

  - Coagulation factor
  - Fibrinolysis
  - Natural anticoagulant

- **Inherited vs Acquired**

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

Female 76-year-old with abnormal bleeding



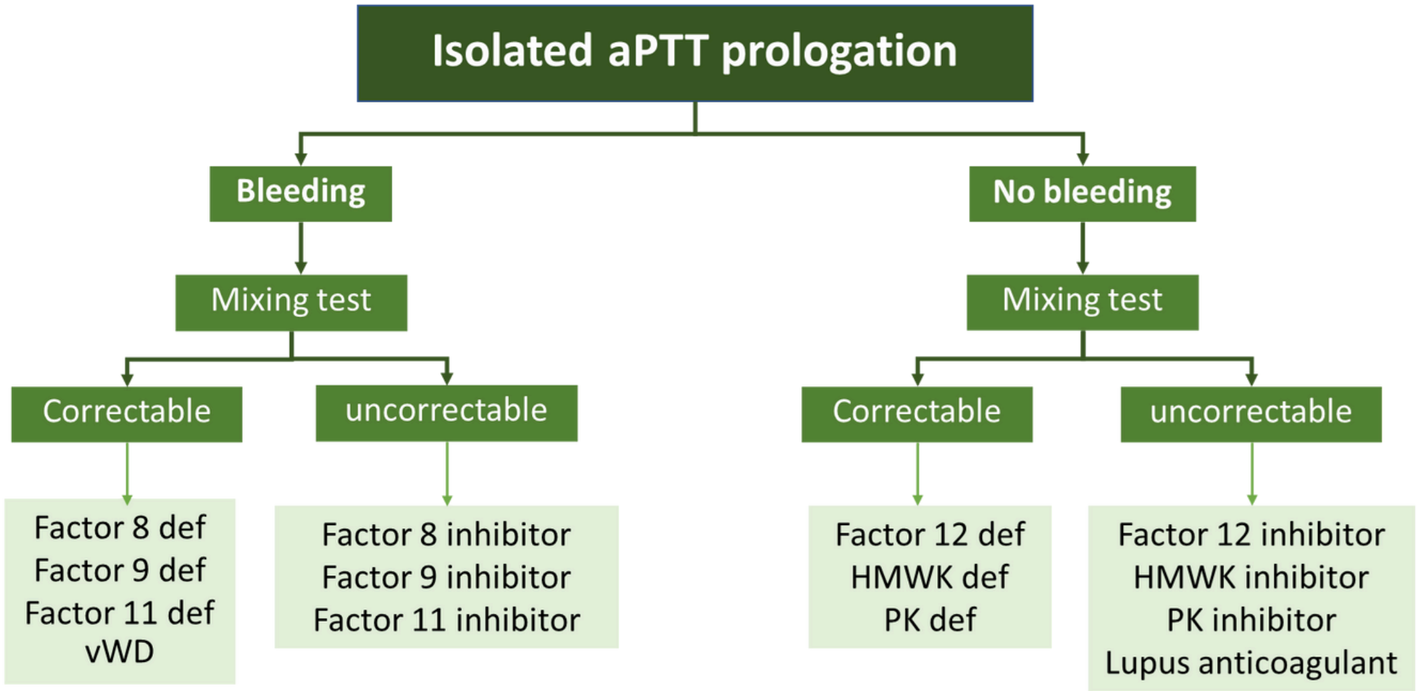
Acquired disorder of secondary hemostasis

Differential diagnosis

- Acquired factor deficiency - DIC, drug
- Acquired factor inhibitor - factor VIII inhibitor
- Hyperfibrinolysis - APL, liver disease
- Acquired VWD
- Paraproteinemia

Female 76-year-old with abnormal bleeding

- CBC : Hb 10.8 WBC 5700 Platelet 270,000
- **APTT 79.0 s**, PT 13.0 s



Mixing test APTT

- At RT = 32 s
- **incubate 2 h = 97 s**

Factor VIII assay - low

Factor VIII Inh - 180 BU

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**, epistaxis)
    - **intramuscular hematoma**
    - Intracranial hemorrhage
    - Postoperative bleeding
    - Postpartum hemorrhage

Acquired hemophilia A

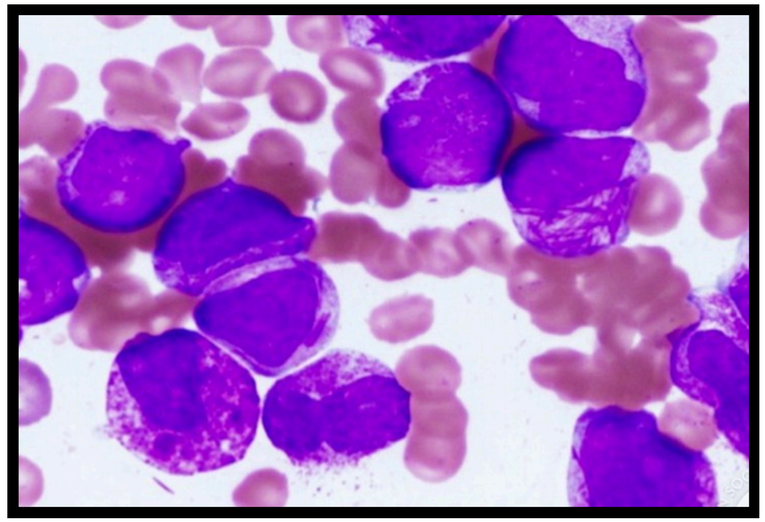
- **Prolonged aPTT**
- **aPTT mixing study fails to correct or re-prolong after 2 h at 37 C**
- Factor VIII activity – low
- Factor VIII inhibitor - detected (Bethesda Unit)
- Management
  - Control bleeding: **bypassing agent**(rFVIIa, aPCC)
  - Eradicate inhibitor: **steroid** +/- cyclophosphamide or RTX

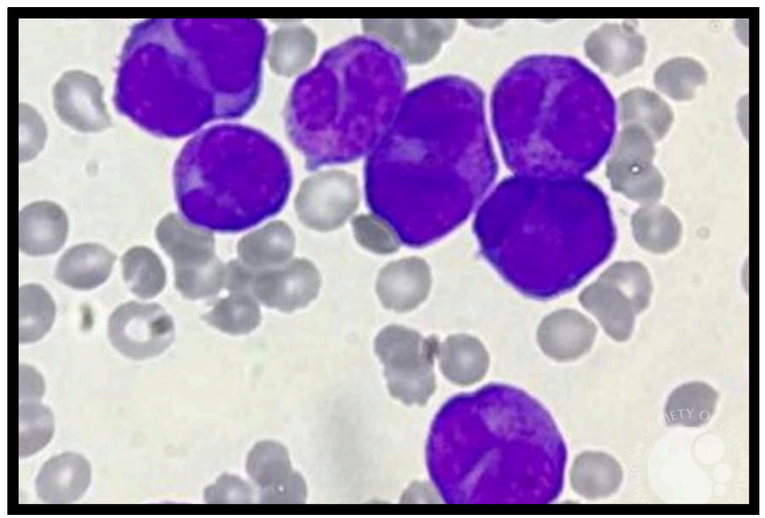
Acute promyelocytic leukemia

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)

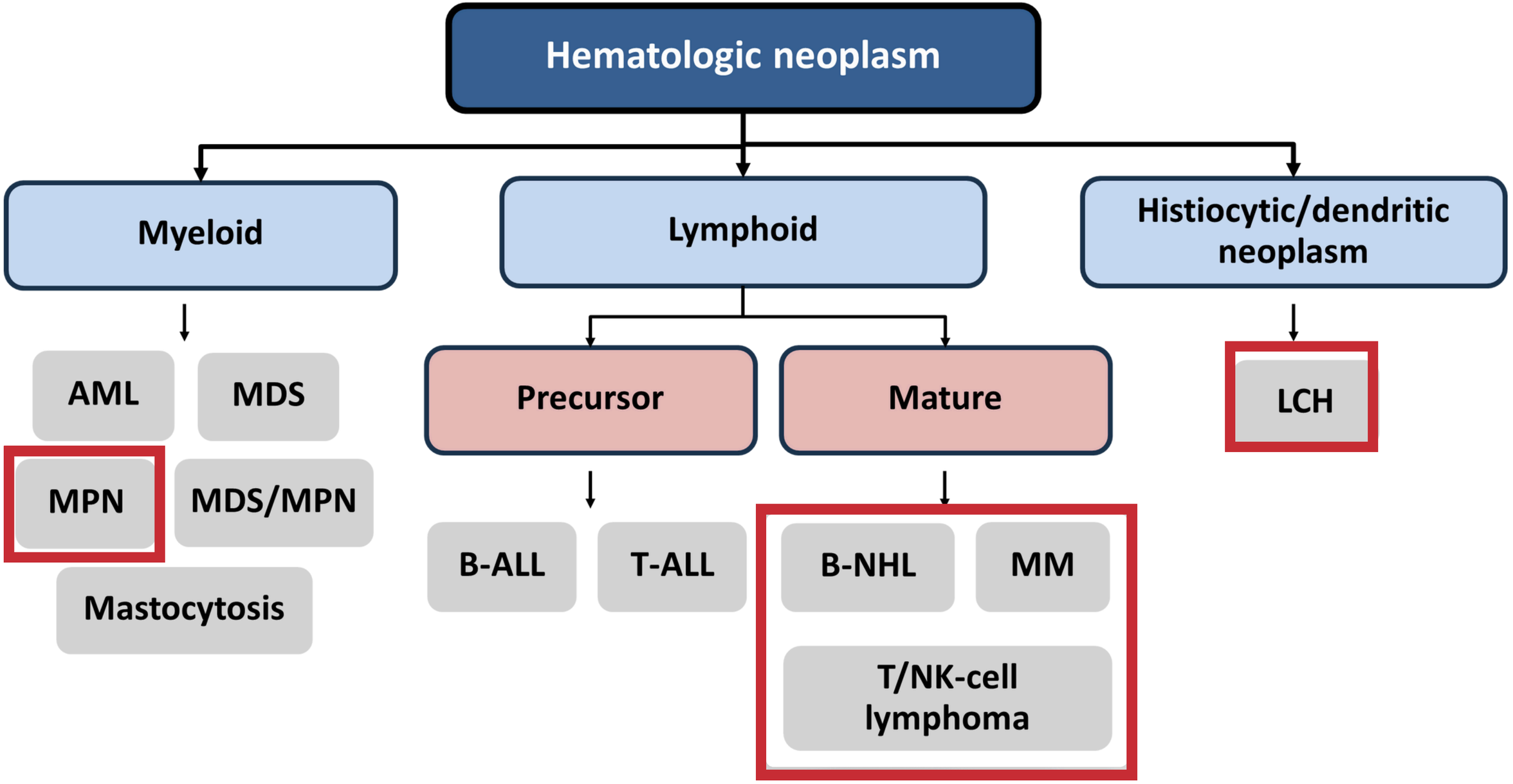
ATRA + Chemotherapy(HR)

Case

- Male 35-year-old with generalized lymphadenopathy for 6 weeks
  - **Lymphadenopathy**
- Male 22-year-old with facial swelling and dyspnea for 2 weeks
  - **SVC syndrome**
- Female 62-year-old with HIV presented with jaw mass for 3 weeks
  - **Jaw mass**
- Male 22-year-old with abdominal discomfort for 1 month
  - **Abdominal mass**

Case

- Male 55-year-old with proptosis and facial weakness for 1 week
  - **Proptosis, facial weakness**
- Male 32-year-old with multiple skin rash for 3 weeks
  - **Skin lesion**
- Female 82-year-old with prolonged fever for 5 weeks
  - **Prolonged fever, FUO**
- Female 52-year-old with Raynaud's phenomenon for 2 month
  - **Raynaud's phenomenon**


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

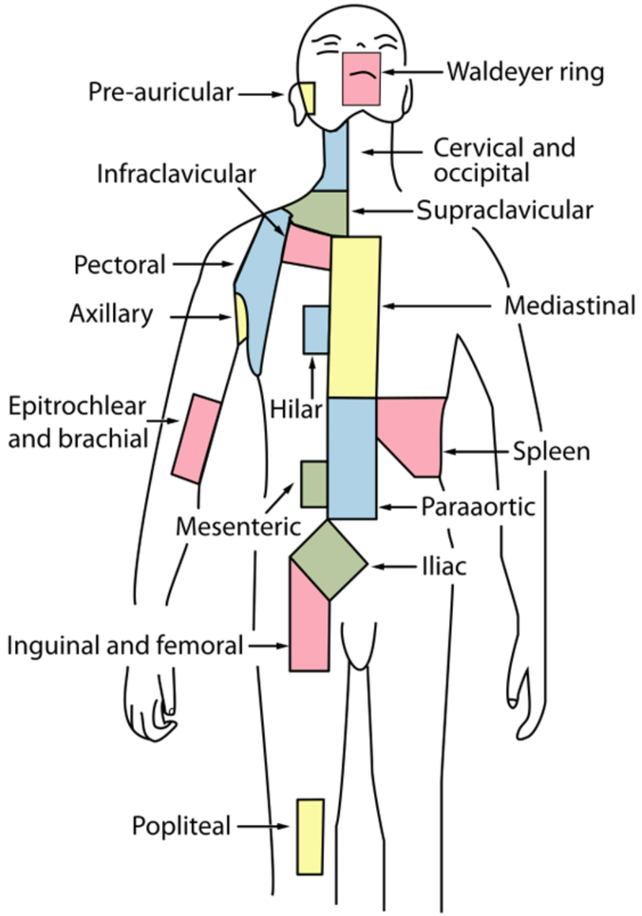
Common manifestations

- **Bone marrow failure**
  - Acute to subacute : AML, ALL, lymphoma with BM involvement
  - Chronic : MDS, MM, PMF
- **Chronic anemia** : MDS, MM, PMF
- **Lymphadenopathy** : lymphoma, ALL, AML M4/5
- **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)
- **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)

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**

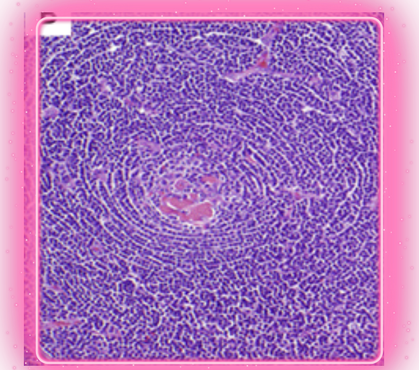
Clinical mimics of lymphoma

- 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

Approach to lymphoma

Hodgkin Lymphoma

- Classical HL
- NLPHL

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

Common manifestations of lymphoma

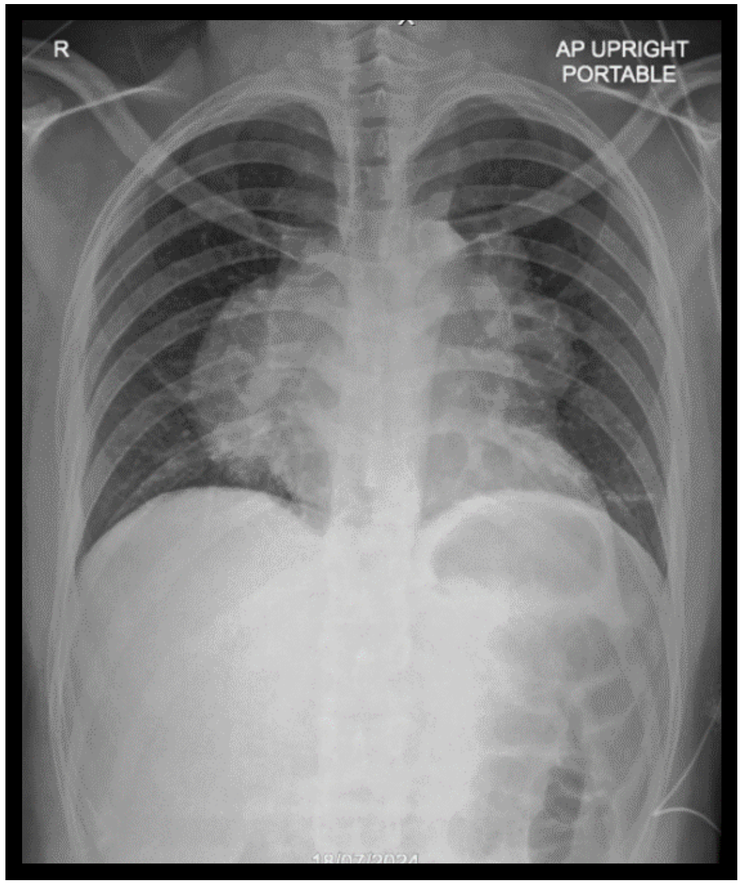
Presentation	Subtypes
Lymphadenopathy	
• Cervical, inguinal , axillary, supraclavicular (most common)	Diffuse large B cell lymphoma (DLBCL), Hodgkin lymphoma, follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, T cell lymphoma (AITL, PTCL, ALCL), etc.
• Mediastinal	Nodular sclerosis 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

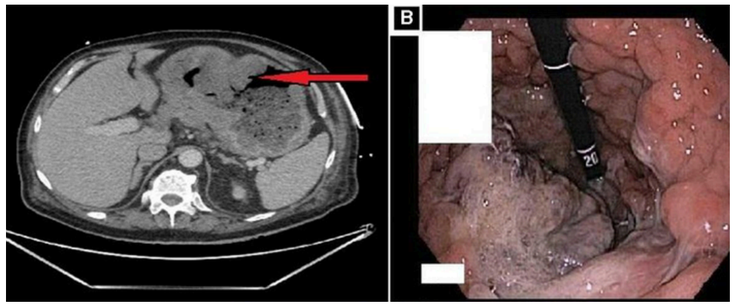
- Dyspnea
- Cough
- Hemoptysis
- Chest pain
- Dysphagia
- Hoarseness
- SVC obstruction



- **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

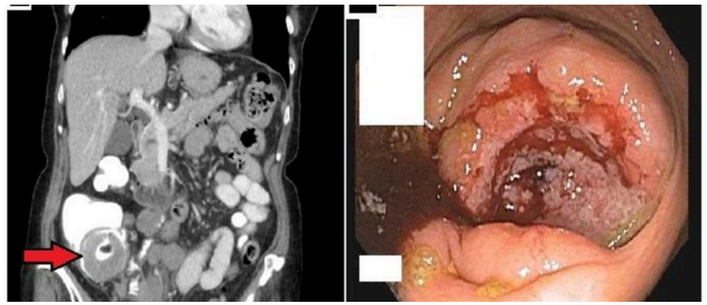


Common symptoms

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

Common subtypes

- DLBCL
- MALT

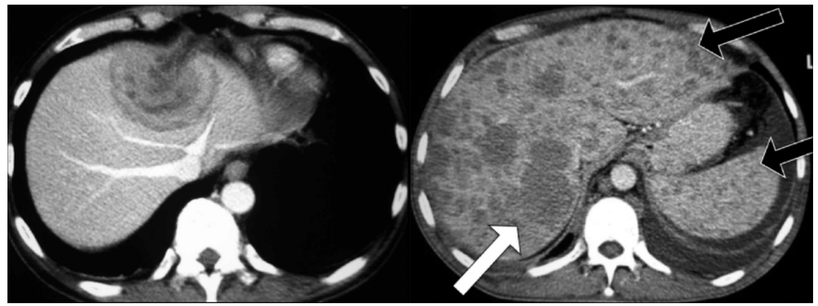


Common symptoms

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

Common subtypes

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



Common symptoms

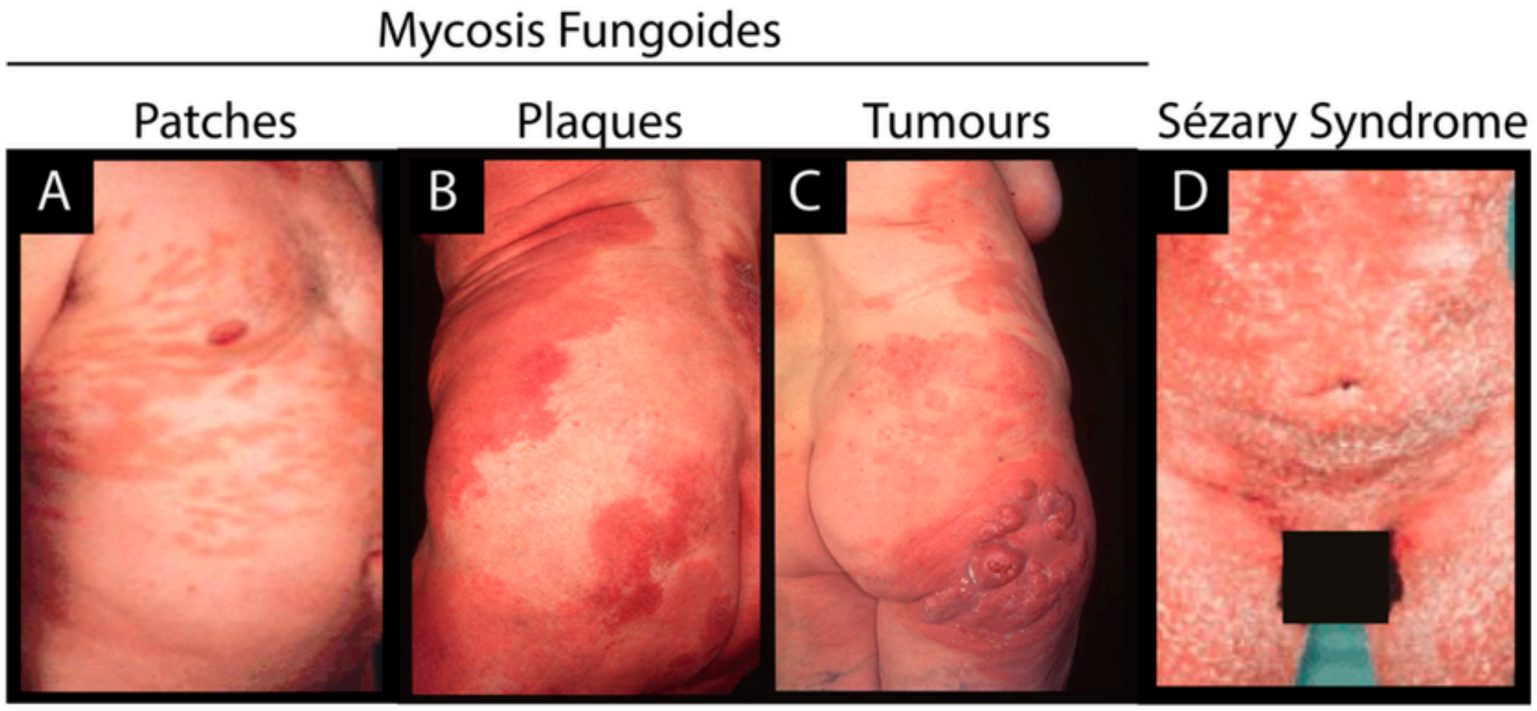
- Hepatomegaly
- Jaundice
- RUQ pain
- Palpable mass
- B-symptoms

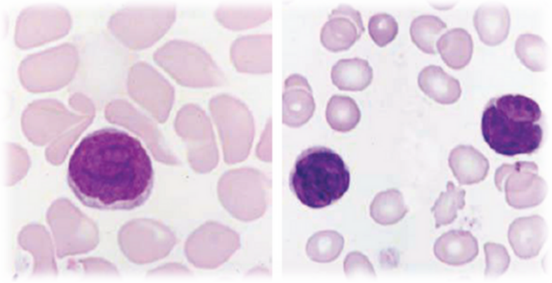
Common subtypes

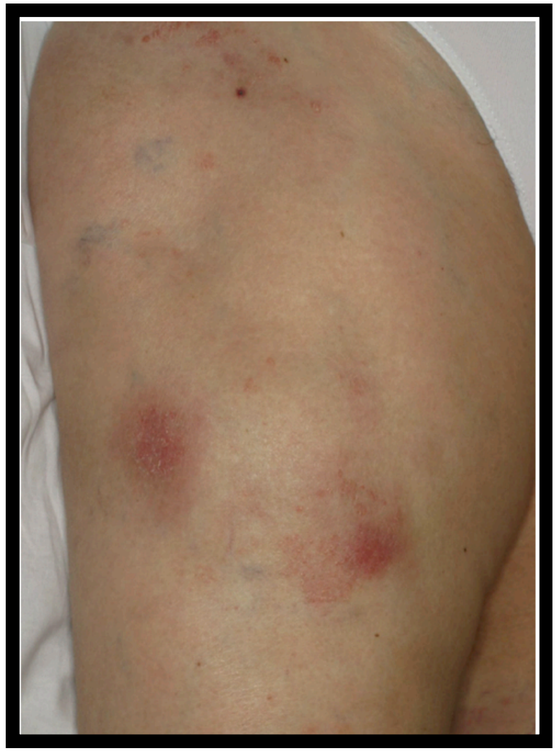
- DLBCL
- MALT, BL, LPL
- Hepatosplenic TCL

MJ Open Gastroenterology 2019;6:e000320

Extranodal lymphoma - Skin







Subcutaneous panniculitis-like T-cell lymphoma

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

Extranodal lymphoma - head and neck

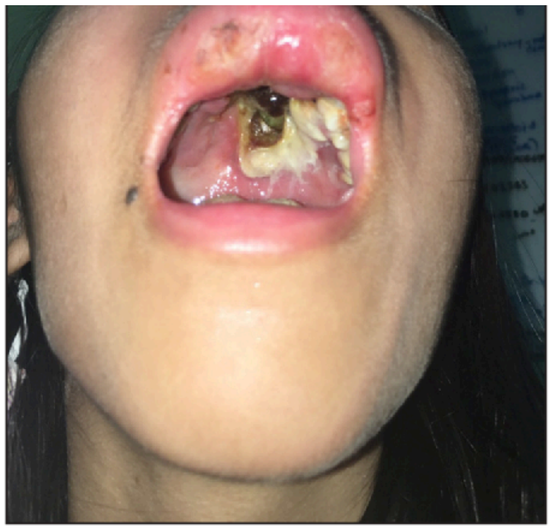
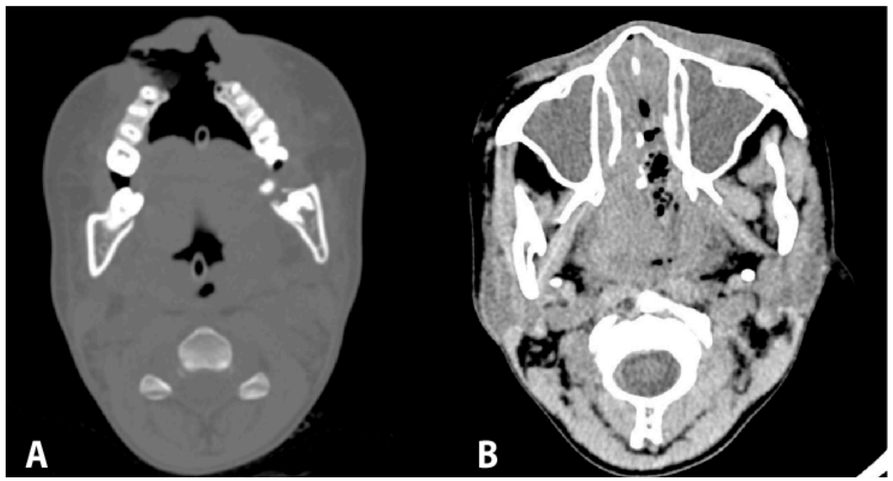


Figure 3. Intraoral view 3 months after initial presentation.



Differential Diagnosis

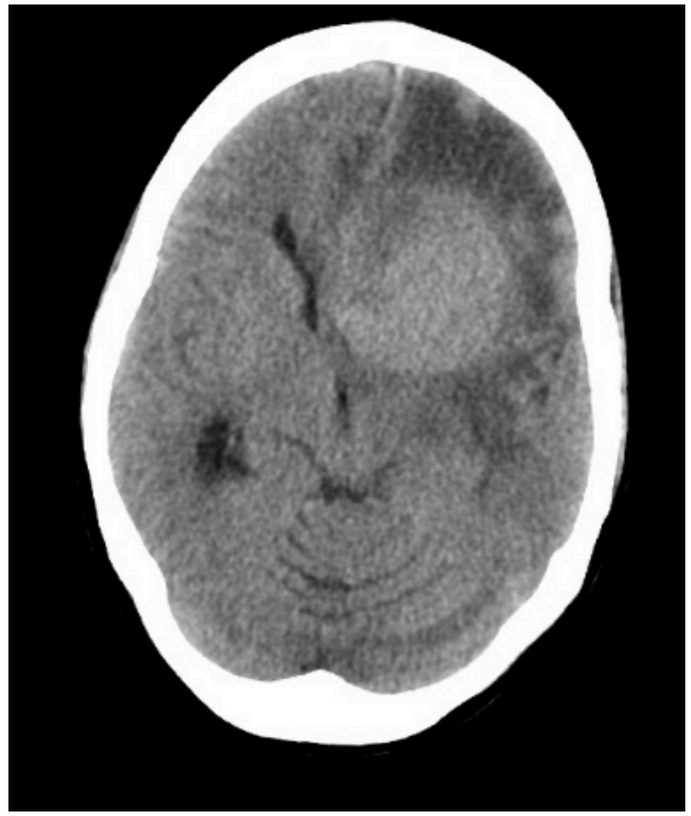
- **Extranodal NK-Cell Lymphoma**
  - B-symptom, organ involvement
- Squamous cell carcinoma
- DLBCL
- Mucormycosis
- Wegener granulomatosis

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

Extranodal lymphoma - CNS

Primary CNS lymphoma

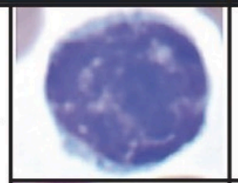
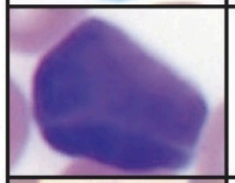
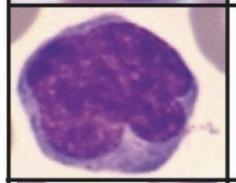
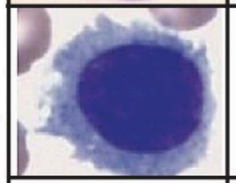
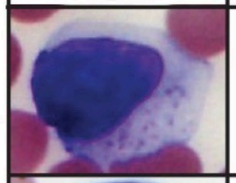
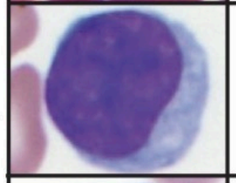
- Most common is DLBCL (90%)
- Most arises in frontal lobe, basal ganglia and periventricular regions
- Most immunocompetent patients have a solitary brain mass (60-70%)
- AIDS-defining illness, usually when CD4 < 50 - multiple necrotic lesion (30-70%)



Extranodal lymphoma – Effusion

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

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**

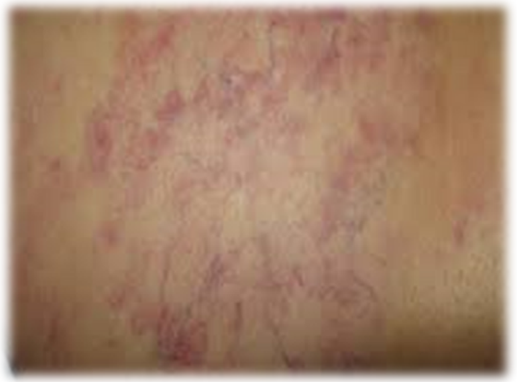
Malignancy **Miscellaneous**

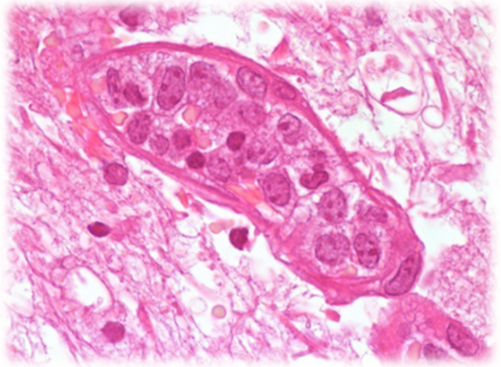
Clues for hematologic malignancy

- Lymphadenopathy
- Hepatosplenomegaly
- Cytopenia
- B-symptoms

Intravascular lymphoma

- Large B cells within the lumen of all sized blood vessels
- FUO, B symptom, organ-specific local symptoms, multiorgan failure, Skin lesion(40%), neurological symptoms(35%)





Blood (2018) 132 (15): 1561–1567.

Approach to lymphoma

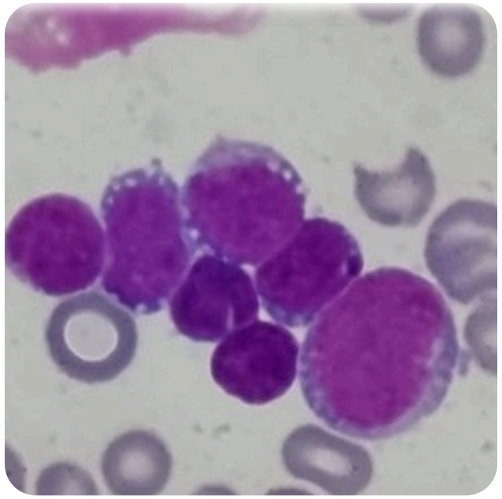
- **Clinical presentation**
  - Lymphadenopathy
  - Extra nodal manifestation
  - Fever of unknown origin
  - Cytopenia
  - Lymphocytosis
  - Hepatosplenomegaly
  - Metabolic disturbance
- **Clinical course**
  - Indolent (> 6-12 months)
  - Aggressive (< 3-6 months)

- **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)

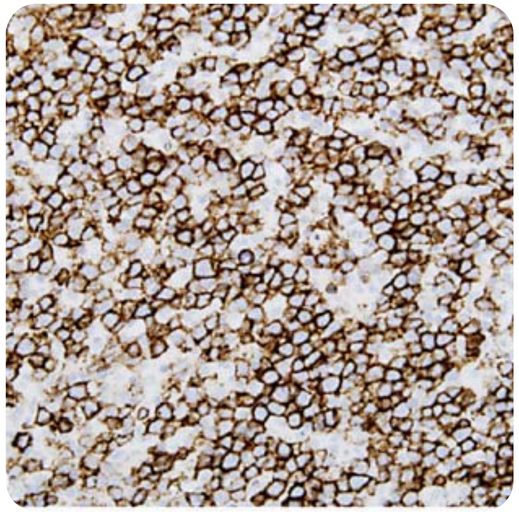
Clinical

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

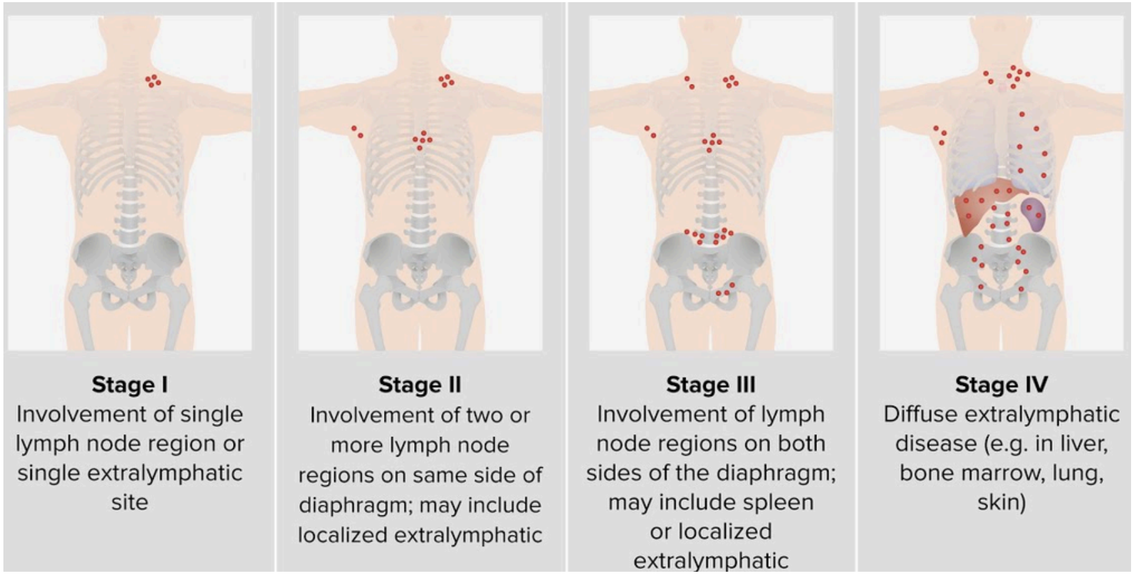


IPI or R-IPI

- **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

Treatment of indolent lymphoma

Localized disease

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

Advanced disease

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

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

Blood Res 2022;57:S120-S129.

Case

- Male 46-year-old with no underlying disease
- Presented with fullness and LUQ pain with symptoms of bone marrow failure for 1 month
- PE: moderate pallor, tip of spleen at umbilicus

BMF with huge splenomegaly

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
  - Endocarditis, brucellosis, syphilis, tuberculosis, histoplasmosis, toxoplasmosis, malaria, leishmaniasis, infectious mononucleosis (EBV), HIV, CMV
- Immune-mediate
  - RA(Felty), SLE, AIHA
- Congestive
  - cirrhosis, PVT, congestive heart failure
- Malignant hematologic

  - Lymphoma, leukemia, MPN
- Nonmalignant hematologic

  - HS, congenital or acquired hemolytic anemias, hemoglobinopathies, extramedullary hematopoiesis
- Infiltrative

  - Gaucher, sarcoidosis, amyloidosis

Massive splenomegaly

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

Lymphoma

- Splenic lymphoma (hairy cell leukemia, splenic marginal zone lymphoma, DLBCL(rare)
- Chronic lymphocytic leukemia

MPN

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

Infection

- Malaria, leishmania

Infiltrative disease

- Gaucher’s disease

Hyperfunction

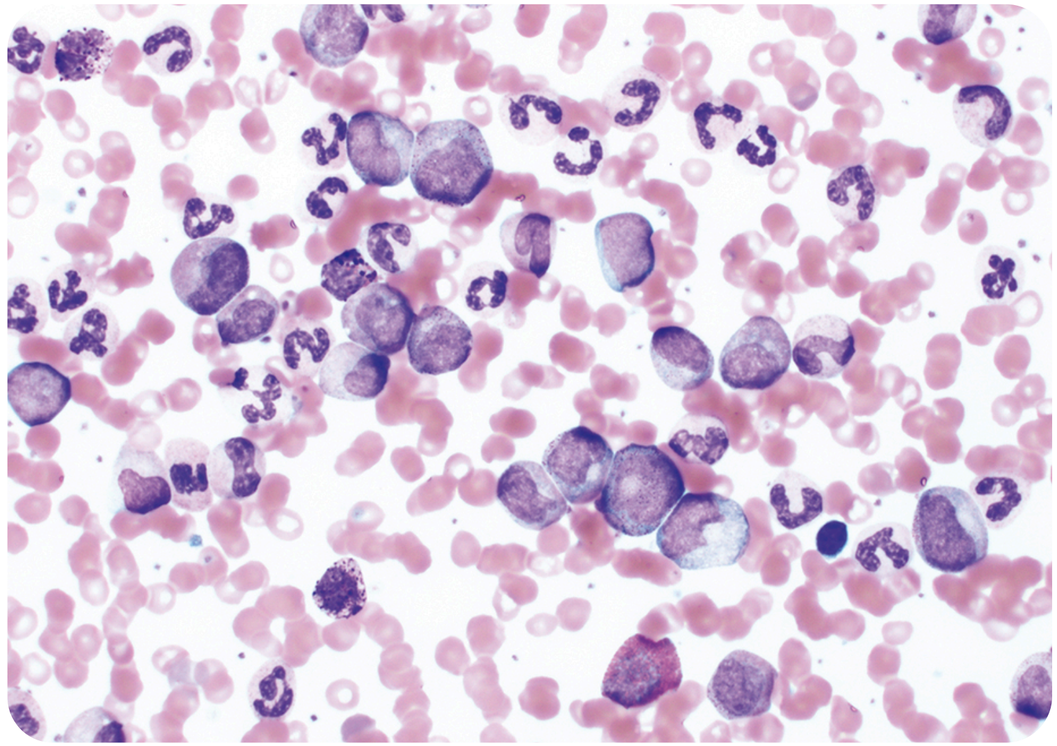
- Thalassemia disease

Chronic myeloid leukemia

- Pathogenesis : t(9;22)(q34.1;q11.2), containing BCR-ABL1 fusion gene
- Diagnosis :
  - Peripheral blood neutrophilic leukocytosis
  - Detection of the Ph chromosome

    +/- BCR::ABL1 by cytogenetic

    +/- molecular genetic techniques



Chronic myeloid leukemia

Common clinical features

- 50% are asymptomatic
- Fatigue, malaise, weight loss
- Anemia
- Splenomegaly - huge

  (easy satiety, LUQ pain)

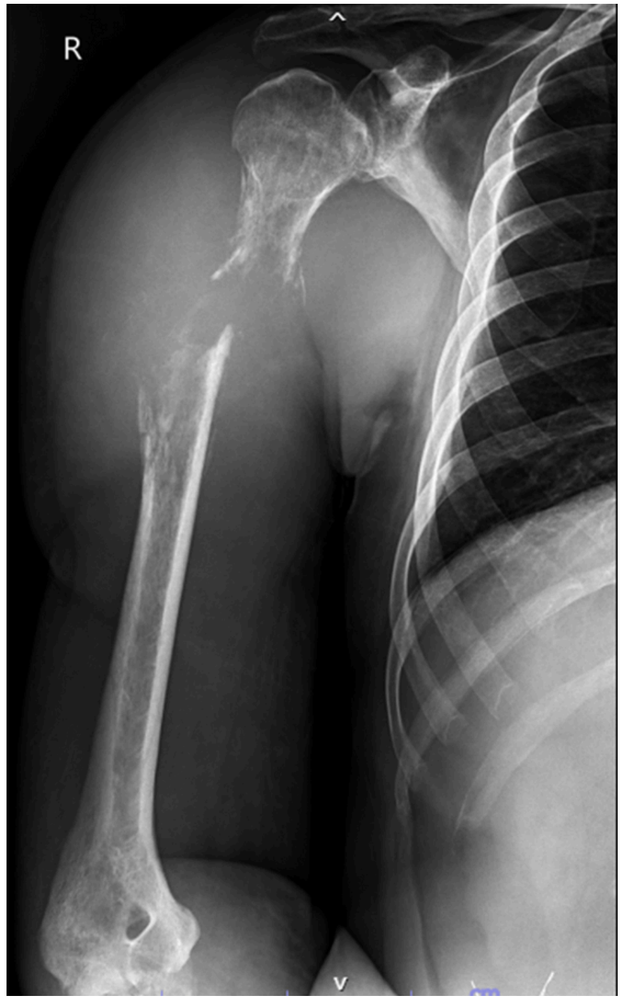
Rare manifestations

- Bleeding (platelet dysfunction)
- Gout (hyperuricemia)
- Visual disturbance

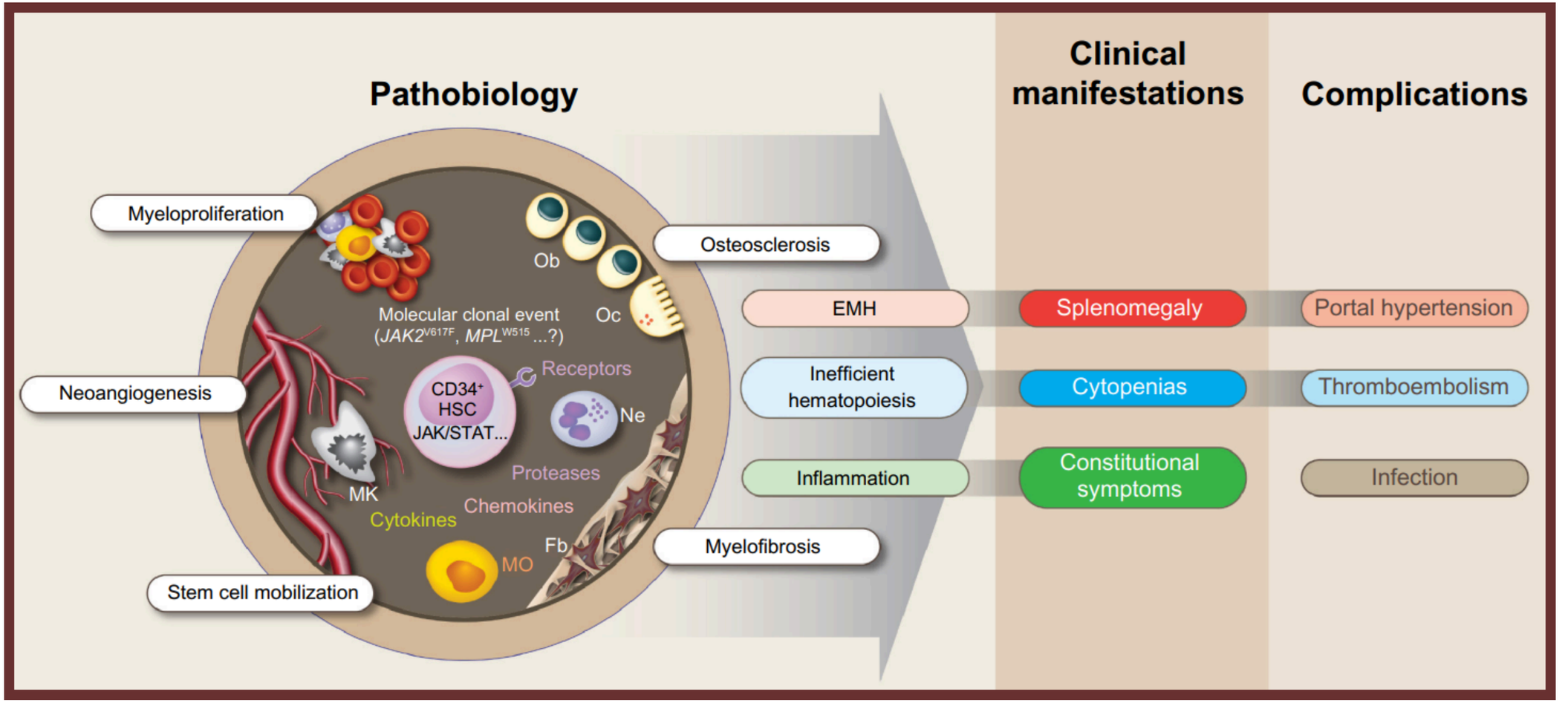
  (hemorrhage, leukemic)
- Thrombosis
- Leukostatic symptoms
- Priapism

When to consider CML BP

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



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

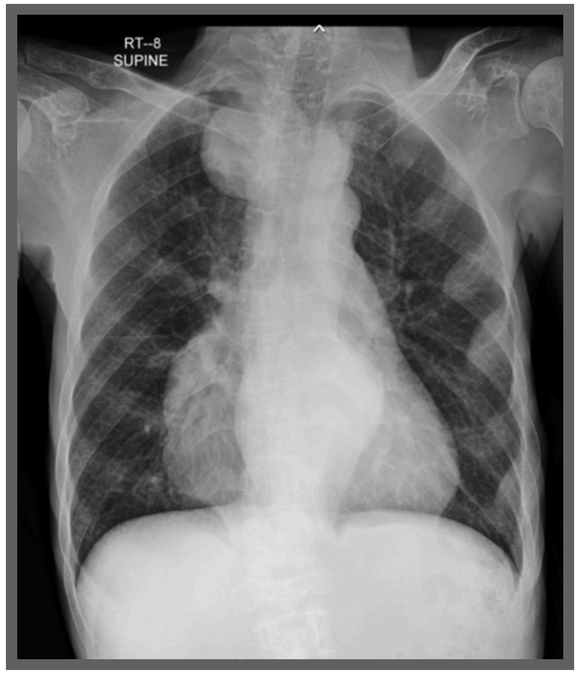
Other manifestations

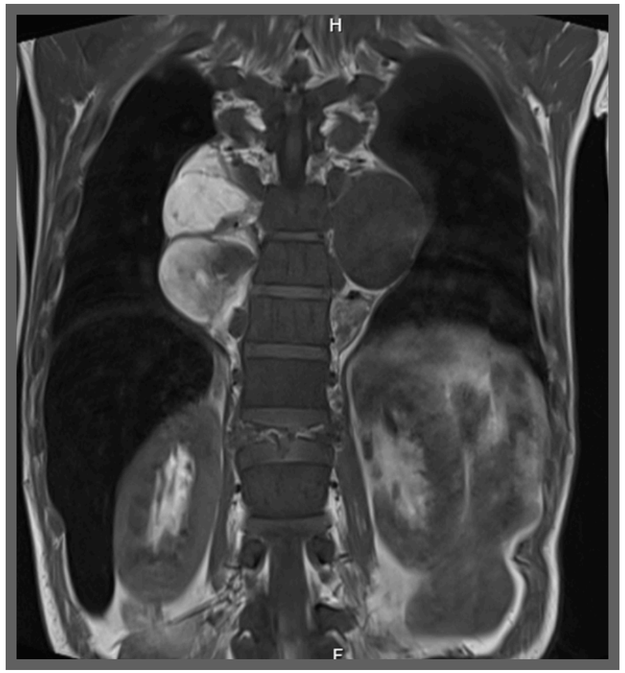
- Non hepatosplenic EMH
- Bone pain
- Splenic infarction (Overt)
- Pruritus
- Thrombosis (splanchnic)
- Bleeding
  - AvWS (Pre-fibrotic)
  - Low platelet, varices (Overt)

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

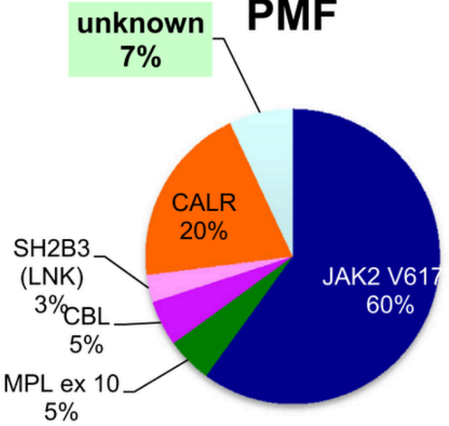
Non-hepatosplenic EMH

- **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.
International Journal of General Medicine 2014:7 89–101

Case

- Female 52-year-old with abdominal pain with jaundice for 2 days
  - **Splanchnic thrombosis**
- Male 32-year-old presented with sudden hemiparesis for 6 hours
  - **Stroke in the young**

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

Athero-sclerosis	Embolism	Meds & substances	Vascular & anatomic	Systemic disorders: Malignancy/ Hematologic	Systemic disorders: Autoimmune	Systemic disorders: COVID-19	Thrombophilias: Inherited*	Thrombophilias: APS
Known risk factors: HTN, HLD, DM, tobacco Review imaging, pathology for atherosclerosis Consider testing lipoprotein(a) [15]	Review imaging for characteristics suggesting embolism TTE with bubble, consider TEE Ambulatory cardiac monitoring	Medication review (Table 2) Review non-prescribed substances Urine screen for cocaine, amphetamines, cannabis	Review imaging for fibromuscular dysplasia, webs, dissection, external compression, vasculitis Consider dedicated arterial imaging	CBC Consider JAK2V617F, PNH, cryoglobulins, hyperviscosity Age/risk-appropriate cancer screening	ESR, CRP, UA Consider autoimmune serologies [43,44]	COVID-19 PCR Recent vaccination, manufacturer	Consider testing if younger (<50-55y), particularly if family history of venous or arterial thrombosis	Consider testing in all patients with repeat at 12 weeks if positive Testing: [38] -aCL IgG, IgM -aβ_2GPI IgG, IgM -LA

PFO
AF

Stroke
MI
PA

JAK2- 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

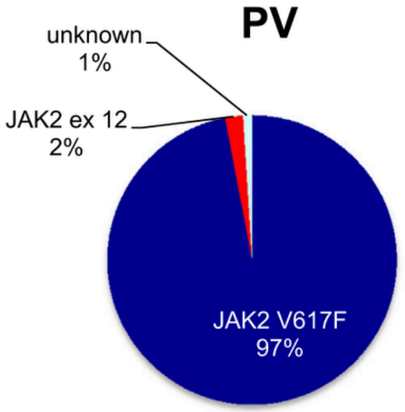
Blood. 2020;135(5):326-334

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



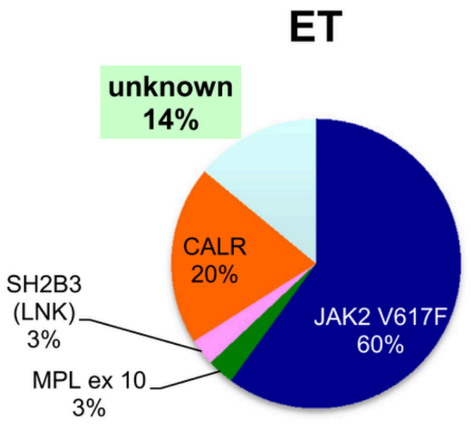
- JAK2-mutated MPN
- Clonal erythrocytosis
- Leukocytosis, thrombocytosis
- Splenomegaly (30%)
- Microcirculatory disturbances
- **Increased risk of thrombosis**
- Progression into myelofibrosis or AML

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

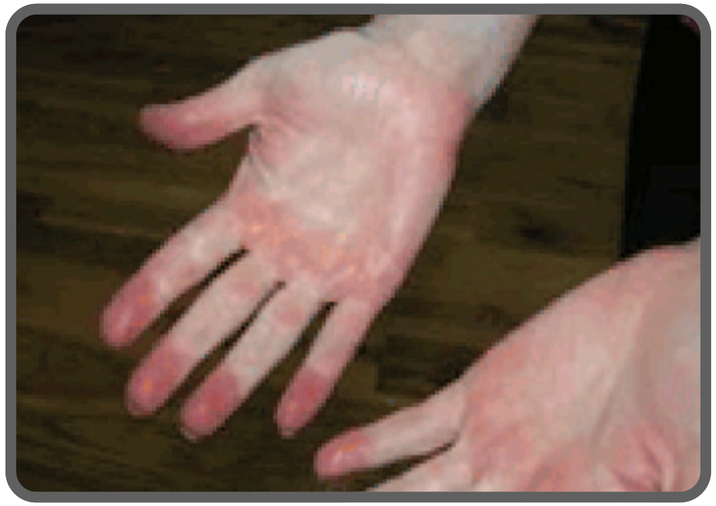
- JAK2 mutation-prevalent MPN
- Clonal thrombocytosis
- **Clinical course - indolent**
- Thrombotic or hemorrhagic complications
- Microcirculatory symptoms
- less frequently, by disease transformation into MF or AML

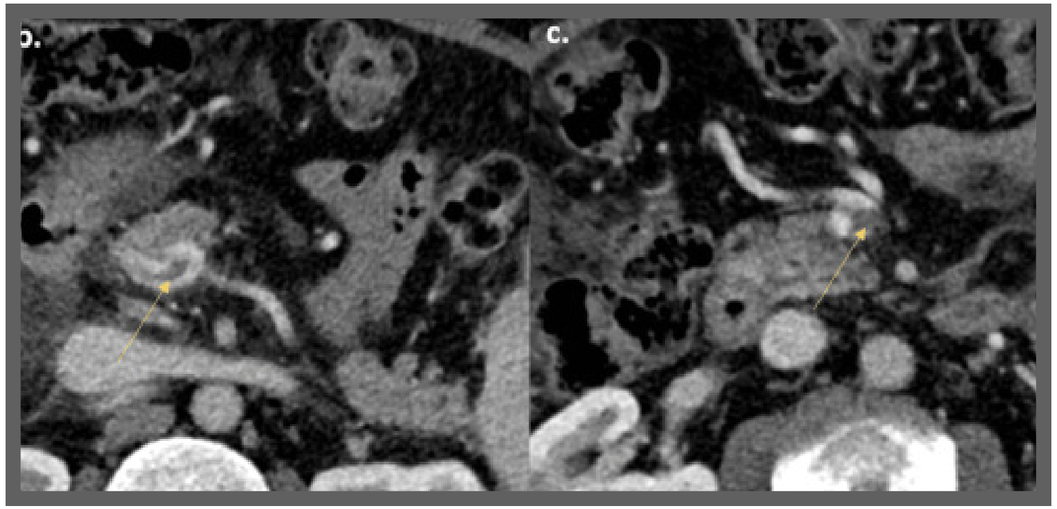


Major criteria:
1. Platelet count ≥ 450 × 10^9/L
2. Bone marrow biopsy showing megakaryocyte proliferation and loose clusters
3. Not meeting WHO criteria for other myeloid neoplasms(CML, PV, PMF, MDS etc.)
4. JAK2/CALR/MPL mutated
Minor criterion:
1. Other clonal marker present
2. No evidence of reactive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

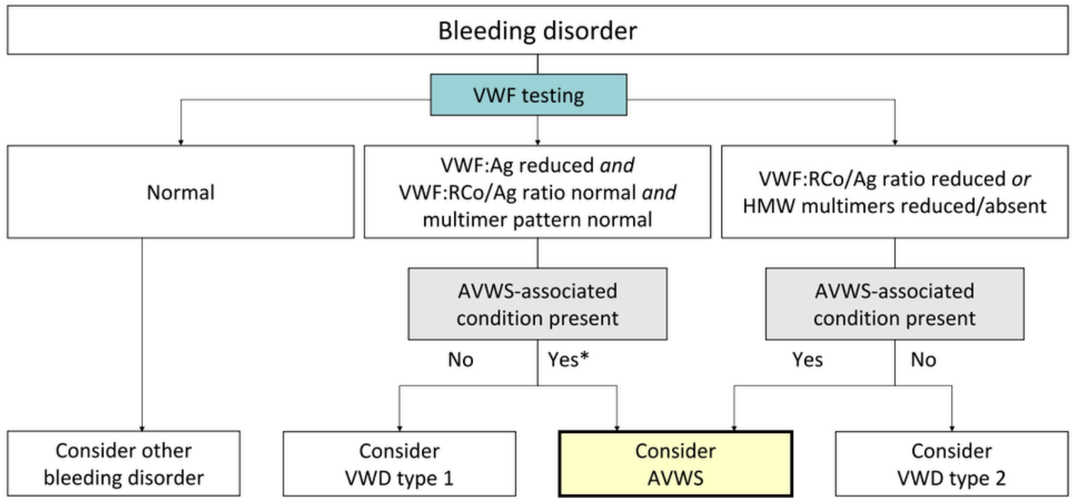
- arterial (15%) - stroke, MI, PAD
- venous (8%) - DVT, PE, unusual sites - rare (CVST, splanchnic)

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 MPN

CML

Chronic phase

First line TKI
- Imatinib

Second line TKI
- Nilotinib
- Dasatinib
- Ponatinib
- Bosutinib

Blast phase

TKI + CMT

PV

Low risk

Age < 60 and no thrombosis

- Low dose ASA
- Phlebotomy

High risk

Age ≥ 60 or thrombosis

- HU
- Low dose ASA
- Phlebotomy

ET

Very low risk

Age < 60, no thrombosis and JAK2 neg

- NO CVD risk : observe
- CVD risk: Low dose ASA

Low risk

Age < 60, no thrombosis and JAK2 pos

- Low dose ASA

Int risk

Age ≥ 60, no thrombosis, no CVD, JAK2 neg

- Low dose ASA

High risk

Age ≥ 60 + JAK2 pos or thrombosis

- Low dose ASA + HU

PMF

IPSS or DIPSS(+)

Low risk or Int-1

- Symptom directed therapy

Int-2 or high risk

- JAK inhibitor
- AlloSCT

Case

- Female 62-year-old presented with paraparesis for 1 week
  - **Spinal cord compression**
- Male 68-year-old presented with blurred vision for 1 week
  - **Visual loss**
- Female 62-year-old presented with foamy urine for 2 months
  - **Nephrotic syndrome**
- Female 65-year-old presented with progressive numbness and weakness at both extremities for 1 year
  - **Polyneuropathy**

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

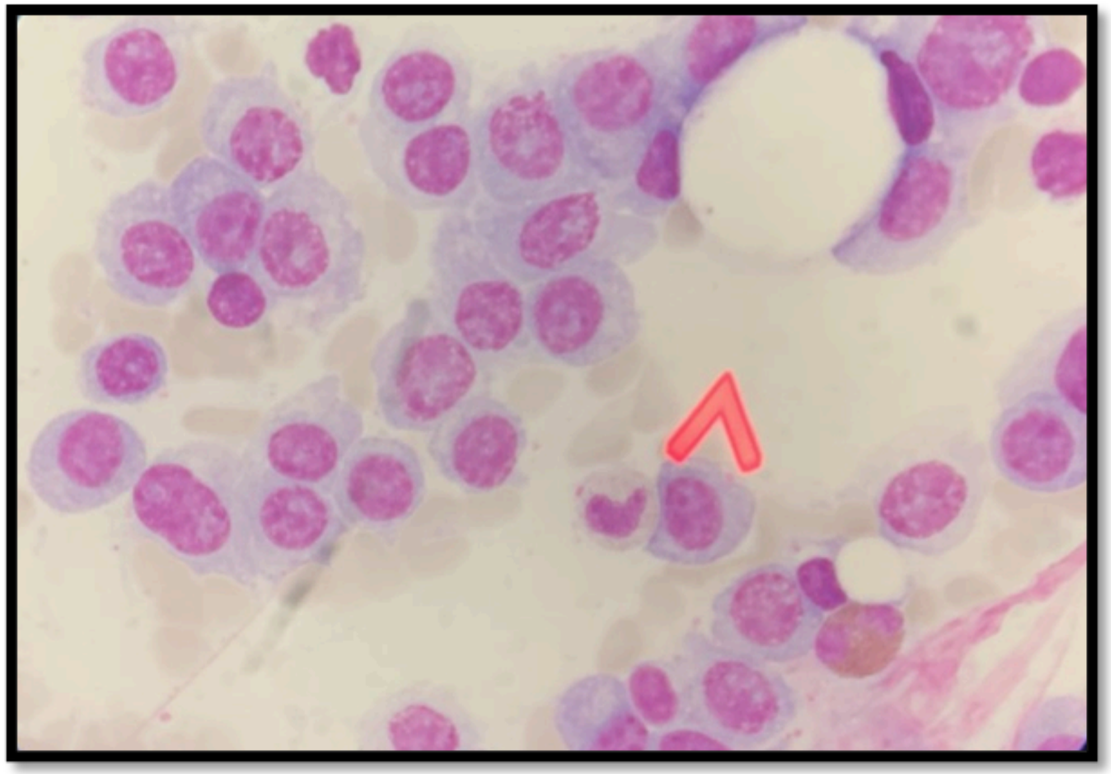
Multiple myeloma

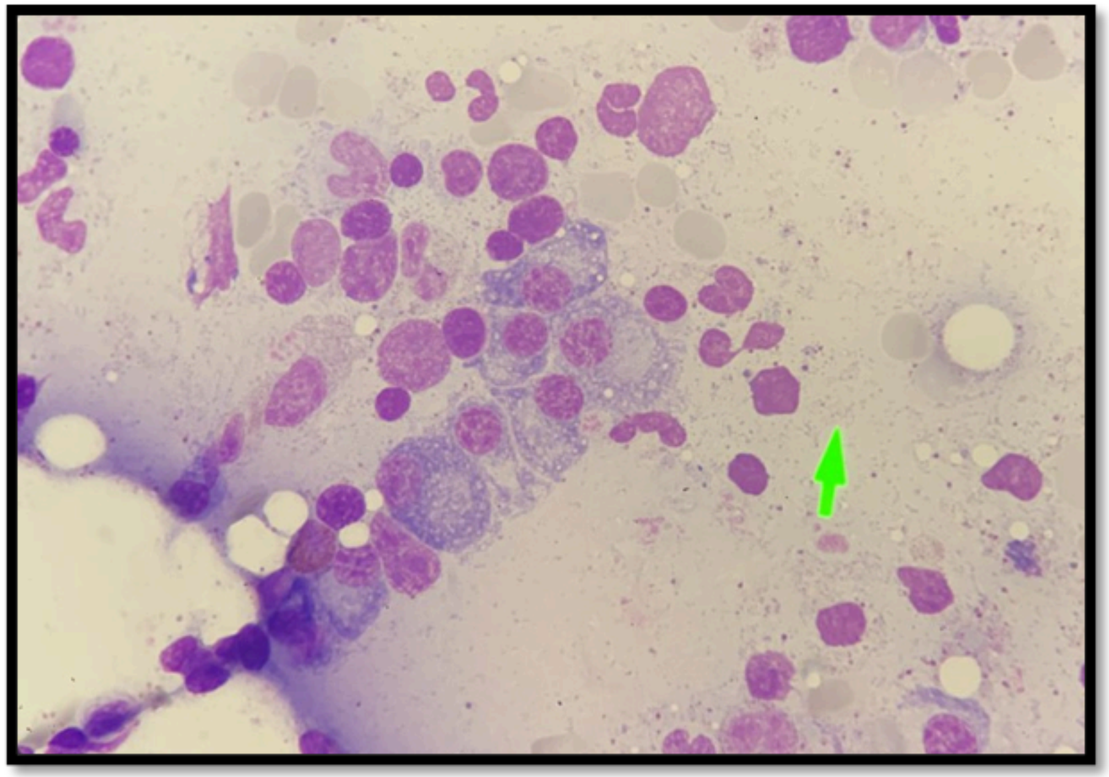
MGUS	Smoldering Myeloma	Active Multiple Myeloma
▪ M-protein < 3 g/dL ▪ Clonal plasma cells in BM < 10% ▪ No myeloma-defining events	▪ M-protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine) ▪ Clonal plasma cells in BM ≥ 10% to 60% ▪ No myeloma-defining events	▪ Underlying plasma cell proliferative disorder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

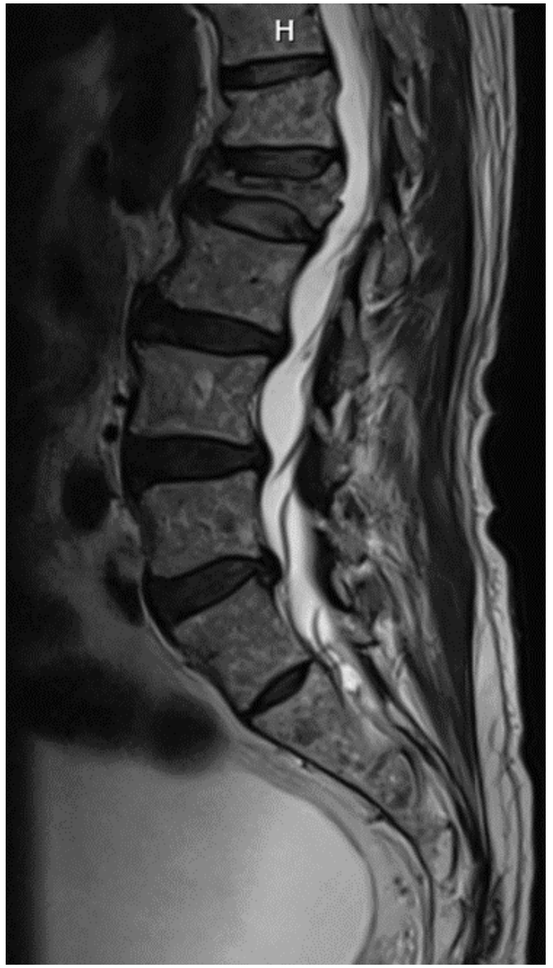




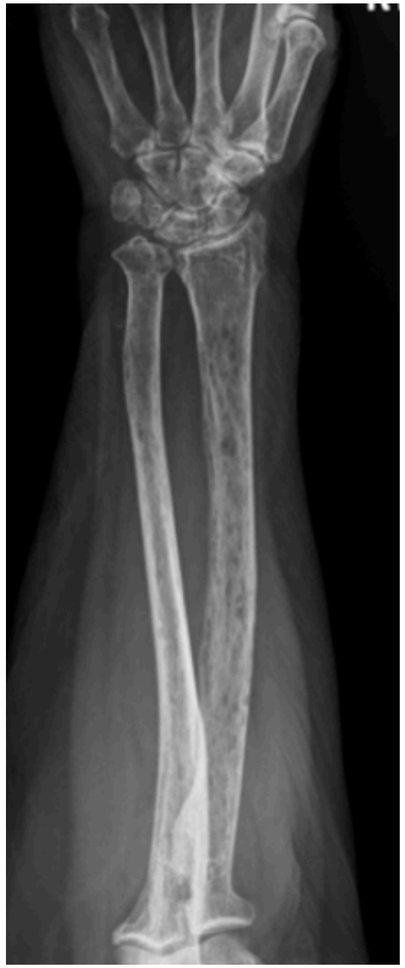
Multiple myeloma

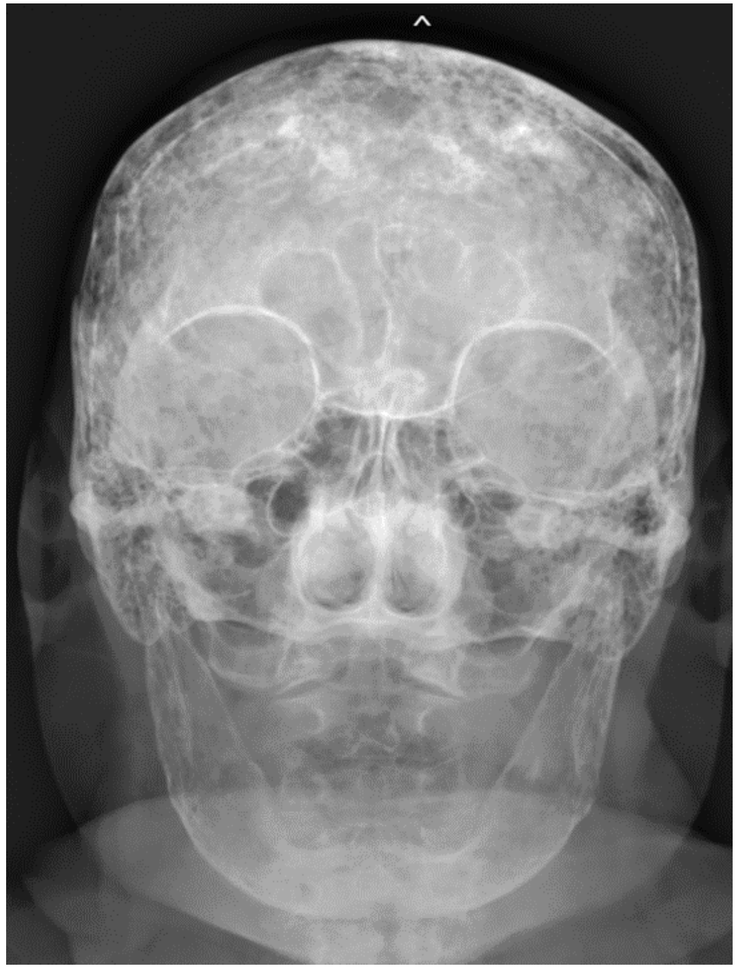
Clinical features

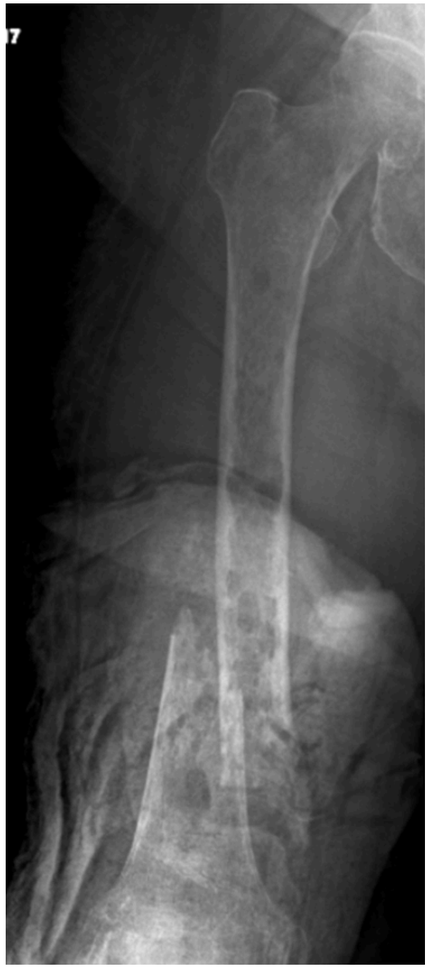
- **Anemia** - fatigue, shortness of breath
- **Skeletal-related events** - bone pain, pathological fractures, spinal cord compression
- **Acute kidney injury** - nausea, confusion, oliguria
- **Hypercalcemia** - constipation, confusion
- **Recurrent infections**
- **Extramedullary disease** - skin and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

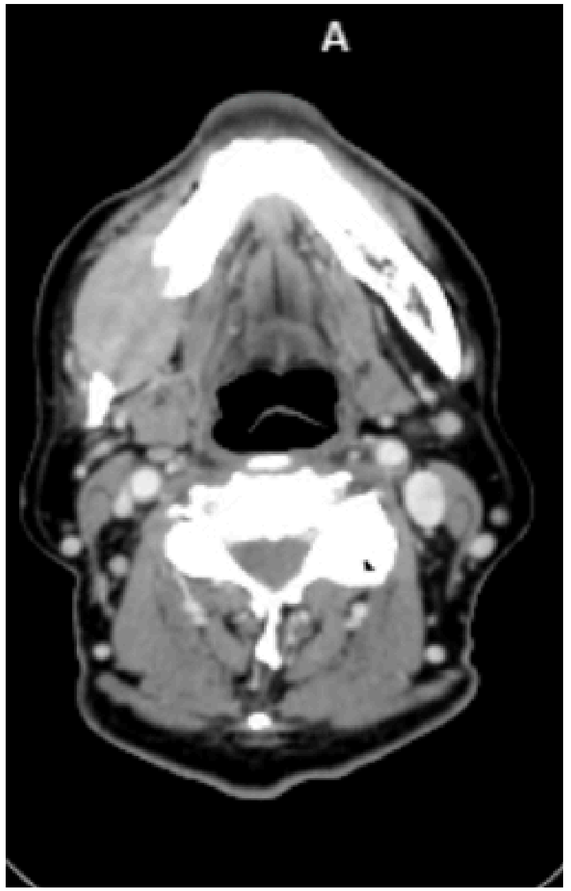


Multiple myeloma

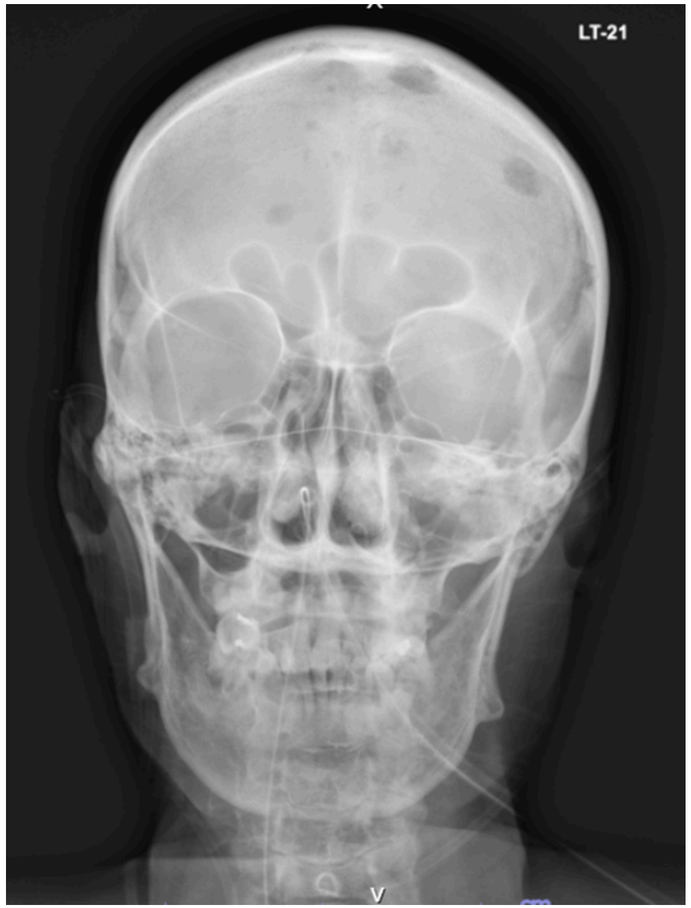




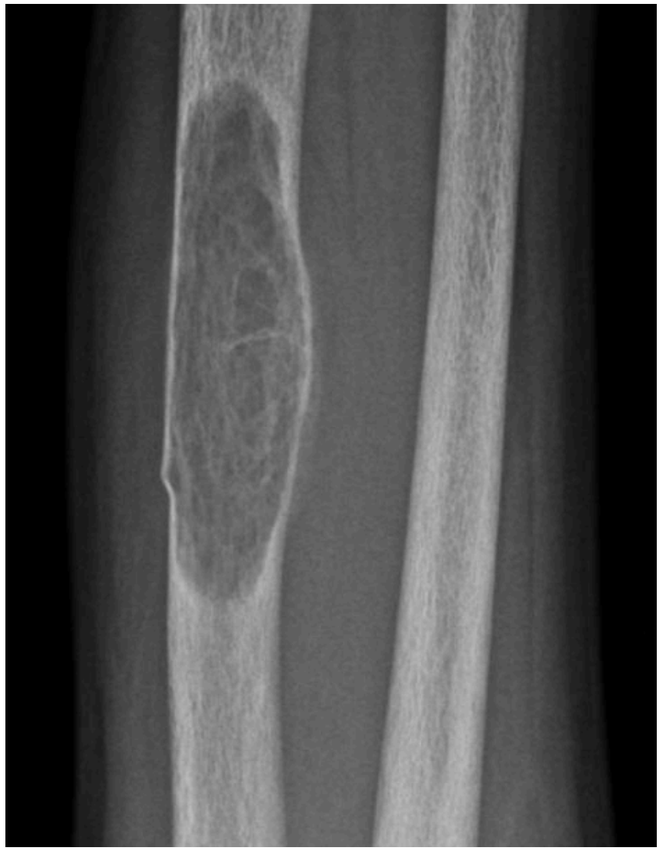




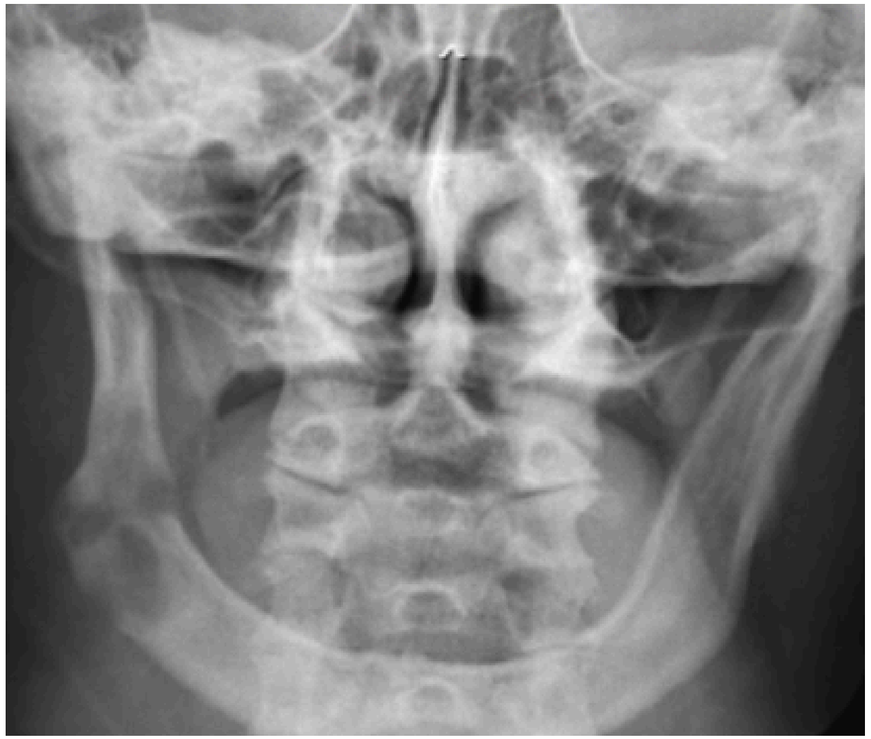
Osteolytic lesion



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)

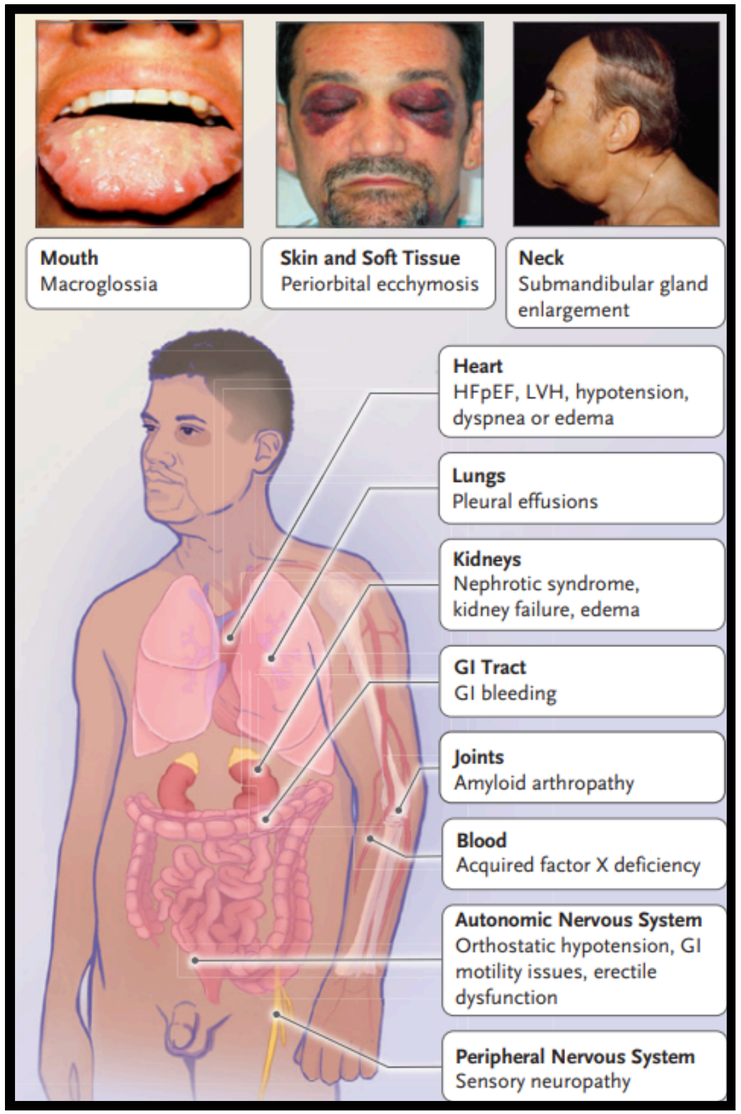
Amyloidosis

- 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, tissue infitration, 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

Liver and spleen

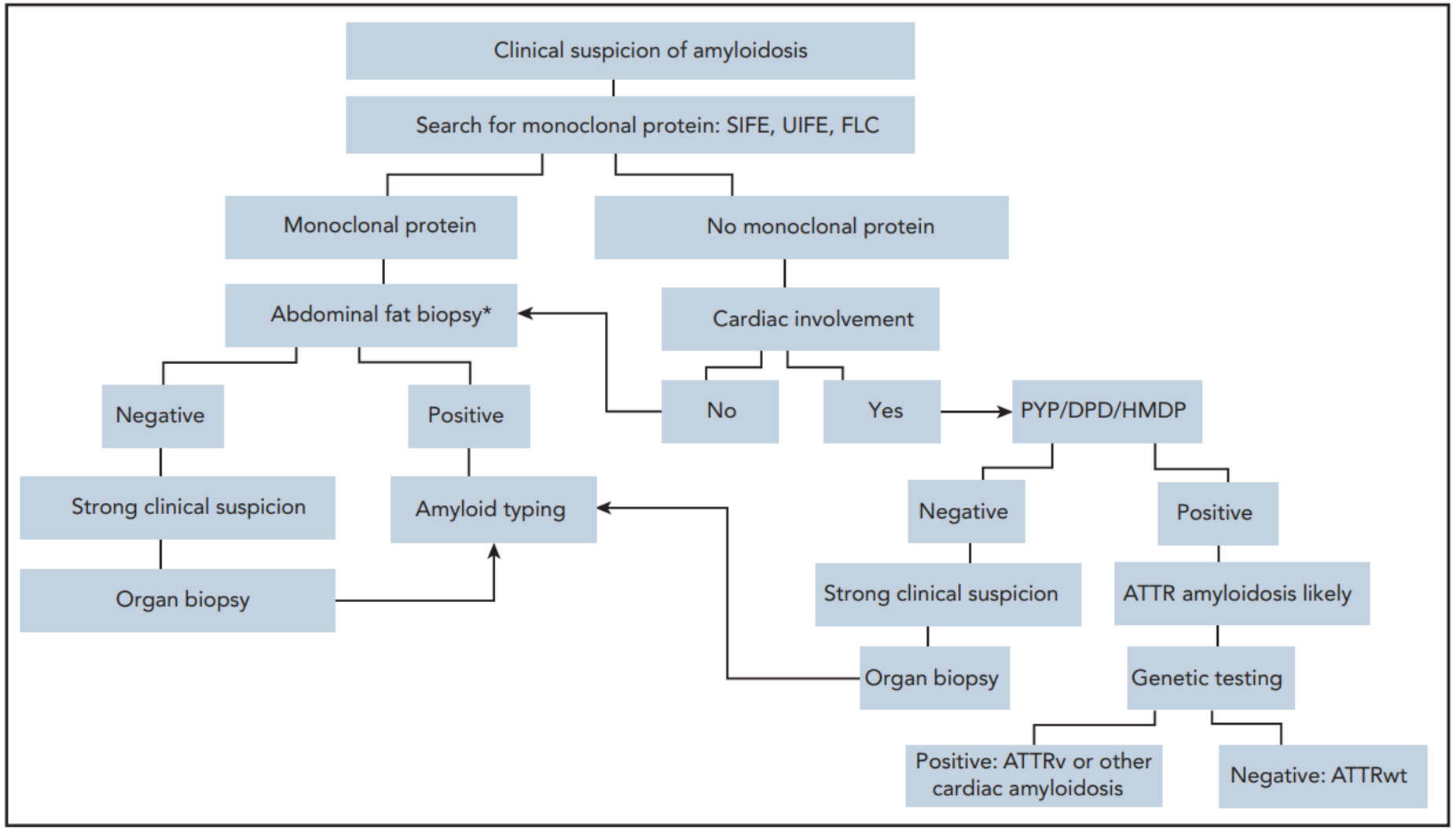
- hepatomegaly, ALP elevation
- early satiety, splenomegaly

PNS and ANS (AL amyloidosis)

- peripheral neuropathy, ED, postural hypotension

n engl j med 390;24

Investigation



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

- Rare paraneoplastic syndrome due to underlying plasma cell disorder

Clinical features

- Long-standing peripheral neuropathy that progressively worsens
  - begin with sensory neuropathy
  - neuropathic pain is common
- Sclerotic bone lesions (95%)
- Endocrinopathies (84%)
  - hypogonadism, hypothyroid
- Hyperpigmentation, hemangiomata (50%)
- Papilledema, peripheral edema (30%)

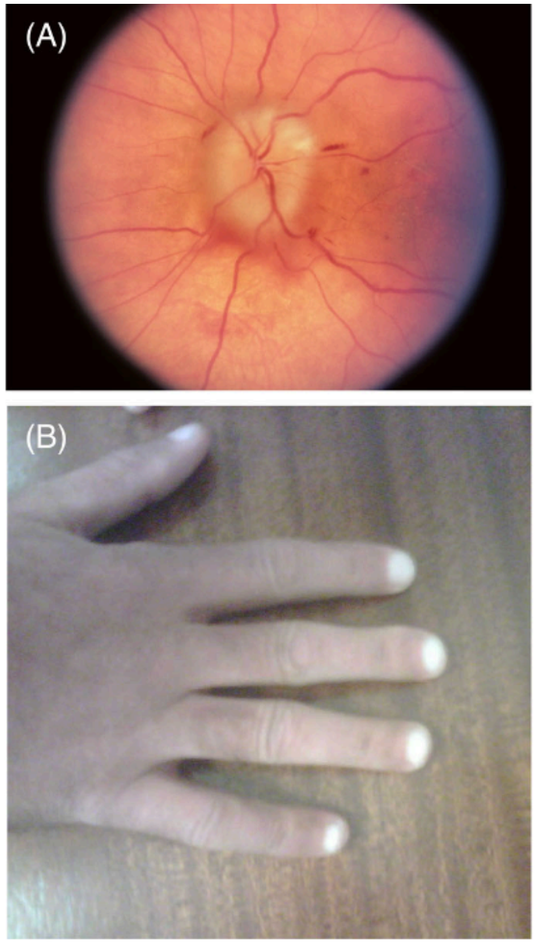
TABLE 1 Criteria for the diagnosis of POEMS syndrome[a]

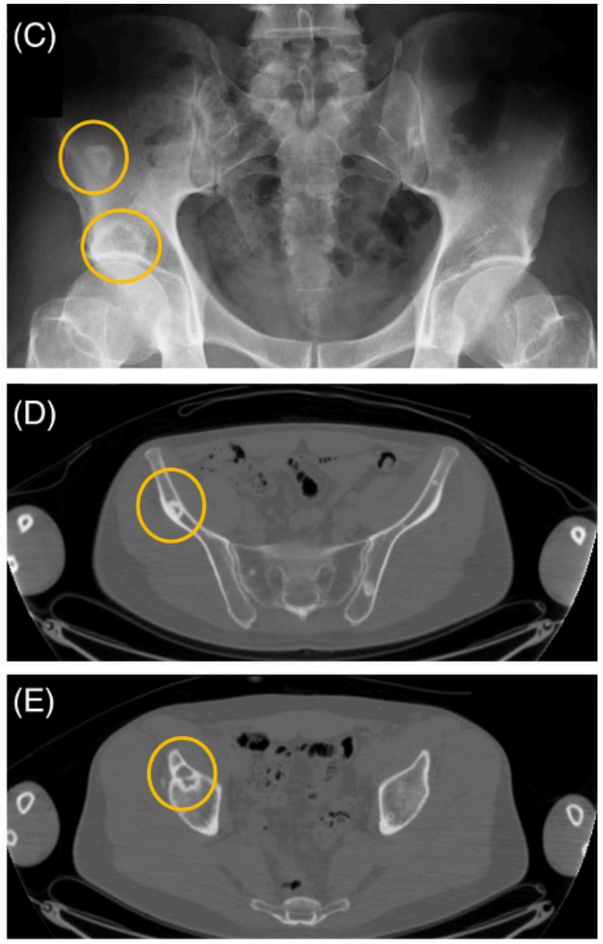
Mandatory major criteria	1. Polyneuropathy (typically demyelinating)
	2. Monoclonal plasma cell-proliferative disorder (almost always λ)
Other major criteria (one required)	3. Castleman disease[a]
	4. Sclerotic bone lesions
	5. Vascular endothelial growth factor elevation
Minor criteria	6. Organomegaly (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.

POEMS

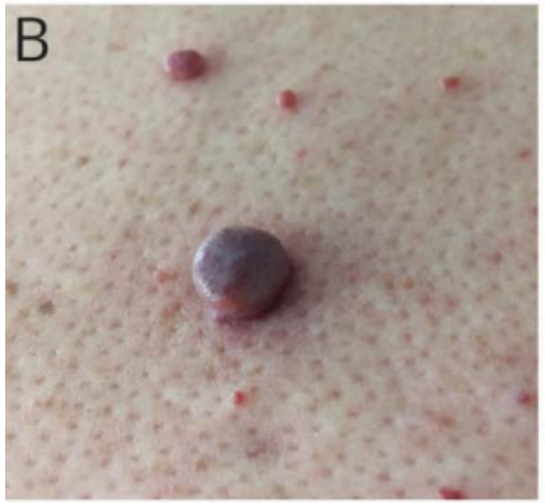
Optic disc edema

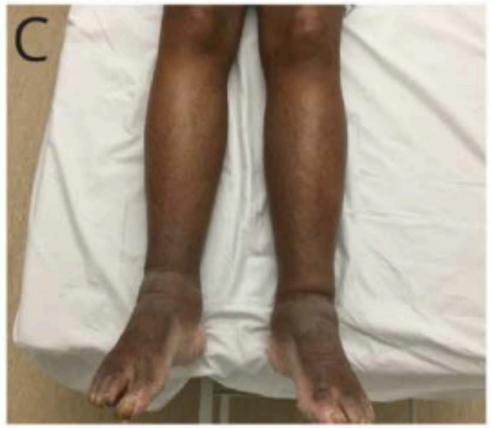


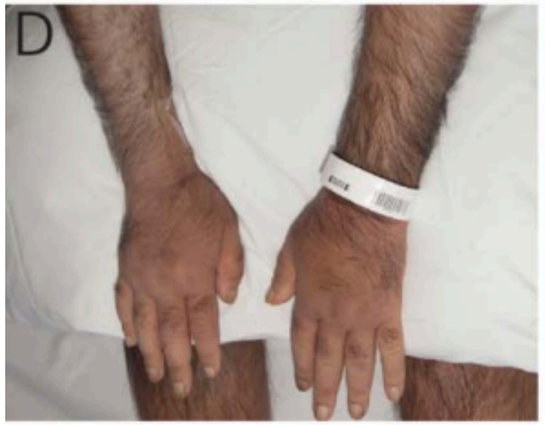


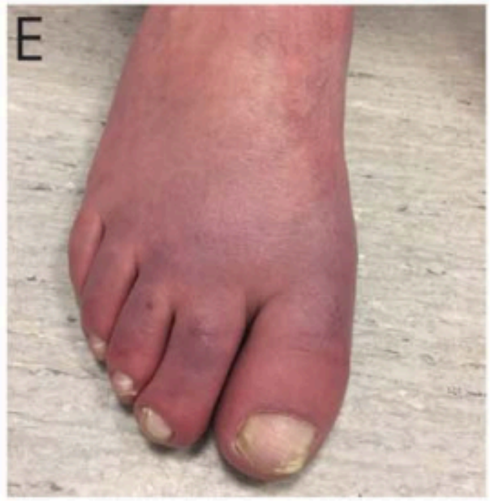
Mixed lytic osteosclerotic bone lesions

Glomerular hemangiomata









Hypertrichosis

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

Waldenström Macroglobulinaemia

Definition

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

Clinical features

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

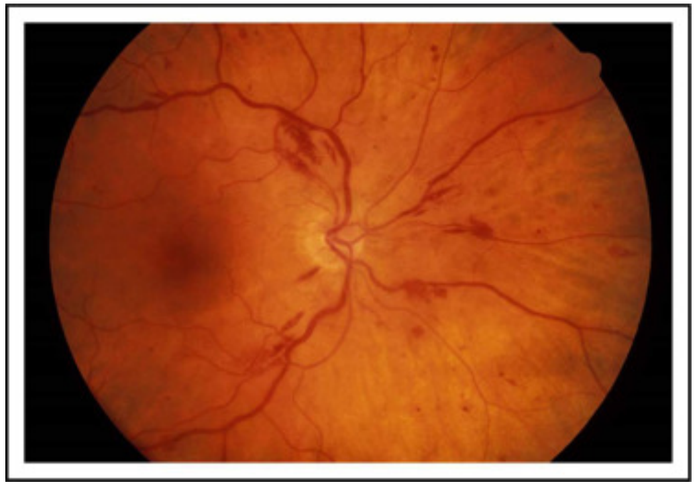
IgM related syndromes

- 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.

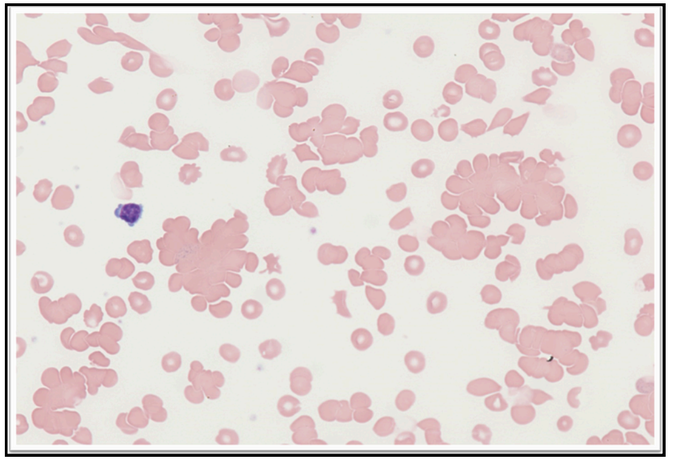
Clinical manifestation

Hyperviscosity syndrome

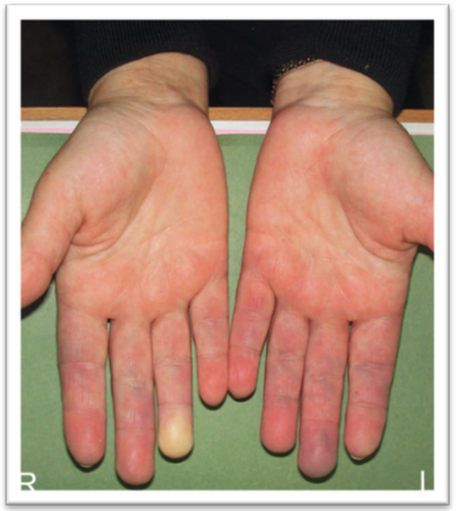


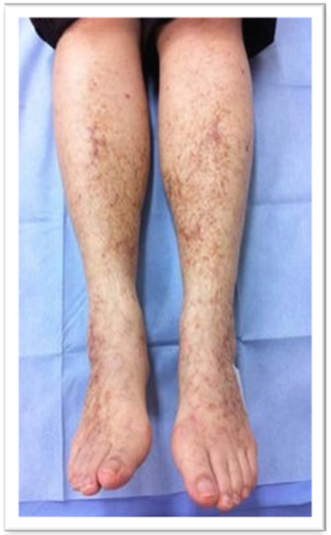
Headache, dizziness, ataxia, blurry vision, retinal hemorrhage encephalopathy, stroke, mucocutaneous bleeding

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

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

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

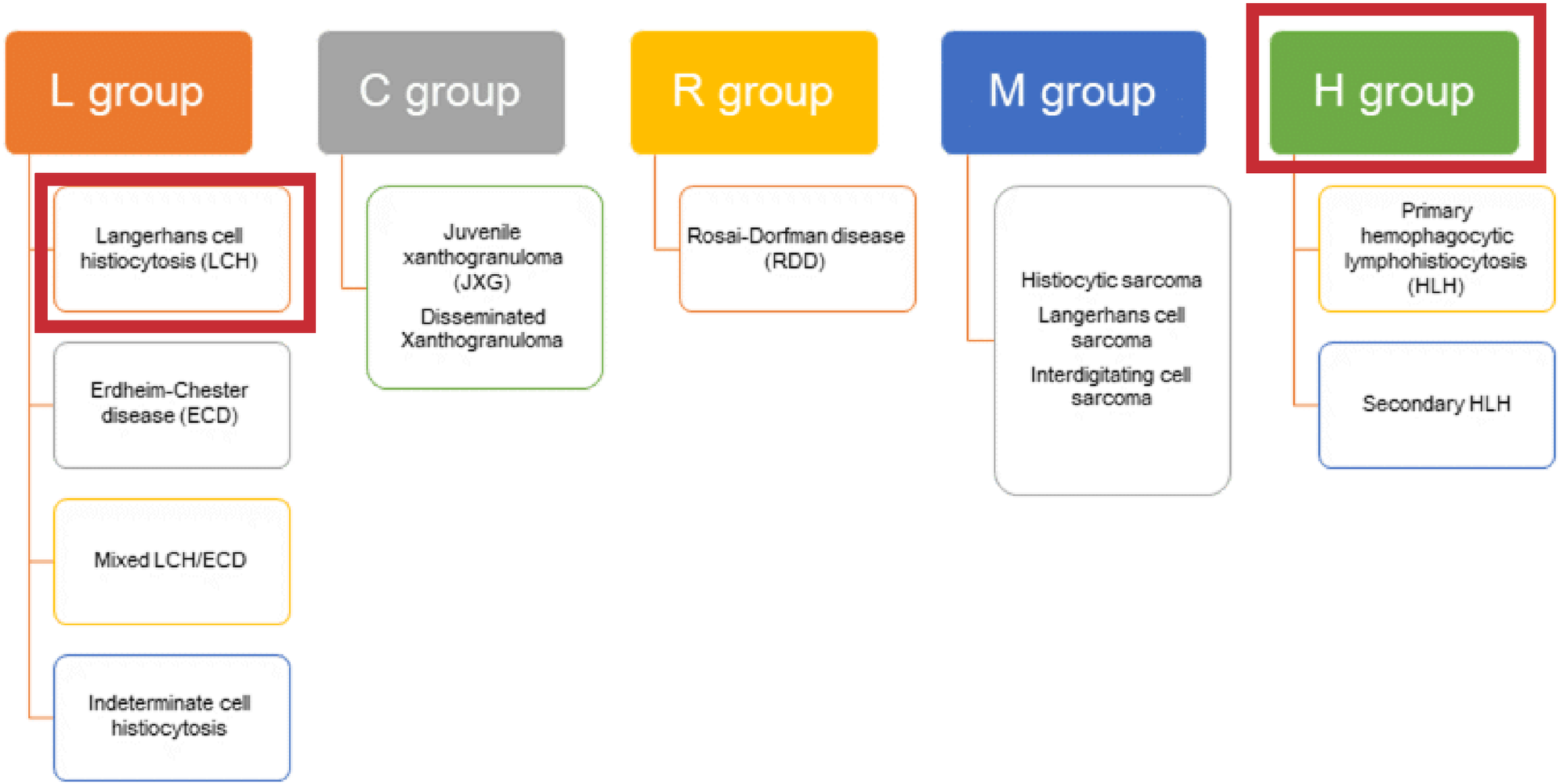
Clinical indications for initiation of therapy
Recurrent fever, night sweats, weight loss, fatigue
Hyperviscosity
Lymphadenopathy: either symptomatic or bulky (≥5 cm in maximum diameter)
Symptomatic hepatomegaly and/or splenomegaly
Symptomatic organomegaly and/or organ or tissue infiltration
Peripheral 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 × 10⁹/L

Blood (2016) 127 (20): 2375–2390.

Case

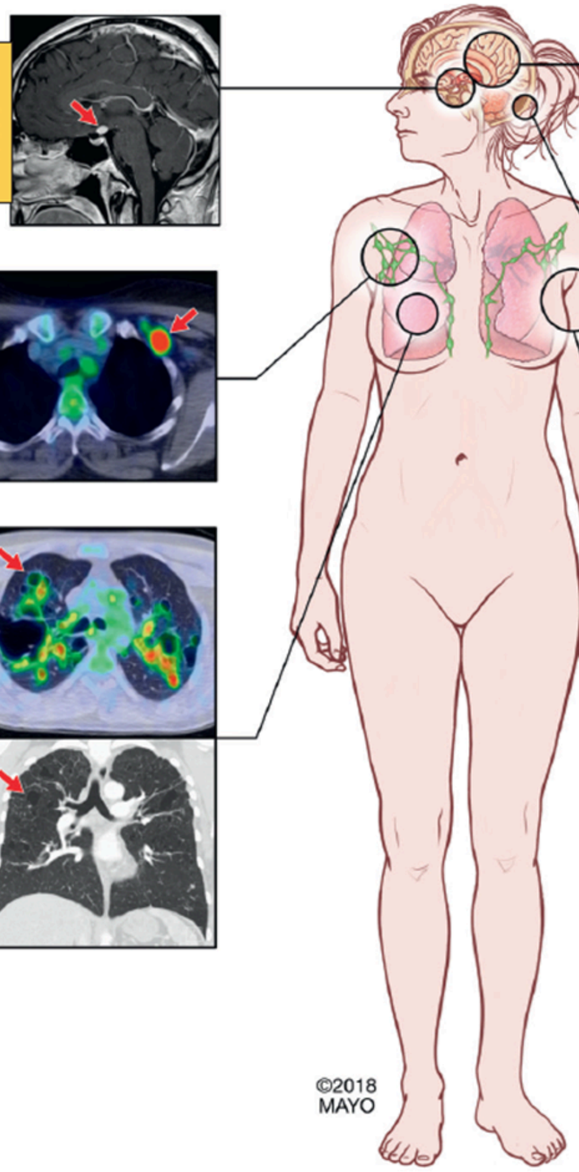
- Female 22-year-old presented with polyuria, secondary amenorrhea for 1 year
  - **Hypopituitarism**
- Male 20-year-old with history of smoking presented with chronic cough for 3 months and spontaneous pneumothorax
  - **Cystic lung disease**

Histiocytic disorders



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

Langerhans cell histiocytosis



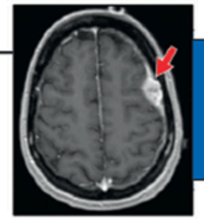
Endocrine - 50%-70%
Most commonly diabetes insipidus, which often precedes diagnosis; hypothalamic and pituitary stalk lesions

Lymph nodes - 5%-10%
Rarely the only site of disease

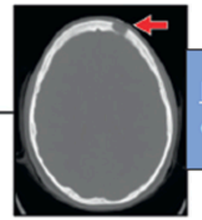
Cervical node, thymus, mediastinal node

Respiratory - 50%-60%
Often in smokers; upper lobe predominant nodules progressing to irregular cysts

- Spontaneous pneumothorax
- Associated w/ smoking

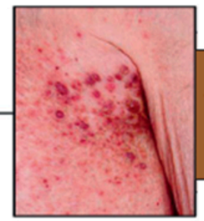


Nervous system - 5%
Dural lesions, often extending from calvarium



Bones - 60%
Osteolytic lesions, often involving skull

may be painful or painless



Dermatologic - 15%-30%
Papular rash, rarely subcutaneous nodules or xanthelasma like lesions

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

Liver
- Hypoalbumin, cholestasis, coagulopathy

Spleen
- Splenomegaly, consumptive cytopenia

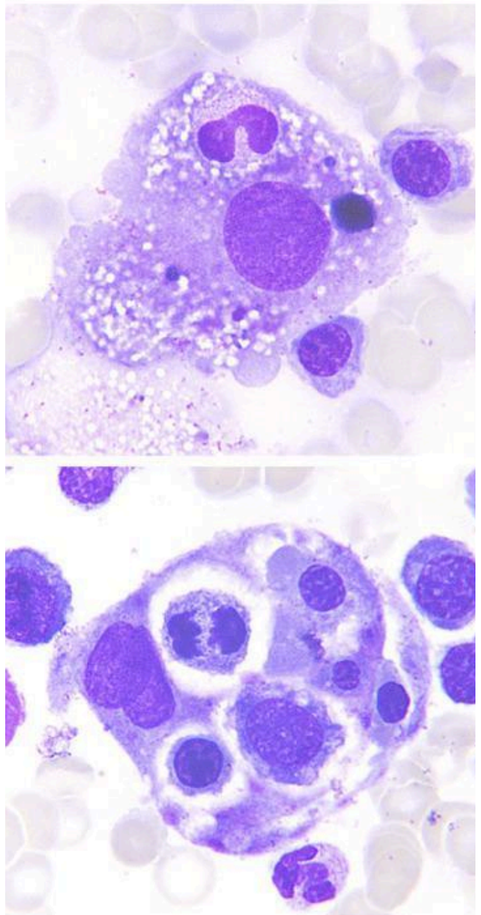
Mayo Clin Proc. 2019;94(10):2054-2071

Hemophagocytic lymphohistiocytosis (HLH)

Clinical - recurrent fever, cytopenia, liver dysfunction, sepsis like syndrome

Table 3. Parameters and points in the HScore

Parameter	No. of points (criteria for scoring)
Known underlying immunosuppression*	0 (no) or 18 (yes)
Temperature (°C)	0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
No. of cytopenias†	0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)
Ferritin (μg/L)	0 (<2000), 35 (2000-6000), or 50 (>6000)
Triglyceride (mmol/L)	0 (<1.5), 44 (1.5-4), or 64 (>4)
Fibrinogen (g/L)	0 (>2.5) or 30 (≤2.5)
Aspartate aminotransferase (U/L)	0 (<30) or 19 (≥30)
Hemophagocytosis on bone marrow aspirate	0 (no) or 35 (yes)



Primary HLH

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

Secondary HLH

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

Blood (2019) 133 (23): 2465–2477.

Hemophagocytic lymphohistiocytosis (HLH)

Primary HLH	HLH-94
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