



Monoclonal Gammopathies:

When the clone is more than a positive laboratory finding (MGCS, MGRS, Neurological)

Ekarat Rattarittamrong, MD

Division of Hematology
Department of Internal Medicine
Faculty of Medicine, Chiang Mai University

Case Presentation

- ▶ **A 33-year-old woman presented with numbness of both arms and feet 5 months PTA**
 - Progressive from toes to lower part of calf and fingers
 - 2 months PTA – difficult to walk
- ▶ **2 hours PTA – anginal pain with pain score 10/10**
 - EKG: STE V1-V4
 - Trop-T hs: 1157 pg/ml
 - Diagnosis: anterior wall STEMI
 - CAG: single vessel disease (LAD), mid thrombus along LAD

Case Presentation

► Physical examination

- **Motor system:** normotonia both upper extremities, hypotonia with muscle atrophy both lower extremities, pes cavus both feet

Upper extremities	Right	Left	Lower extremities	Right	Left
Neck flexion/extension	V/V	V/V	Hip flexion/extension	III/III	III/III
Shoulder abduction	V	V	Hip abduction/adduction	IV+/IV+	IV+/IV+
Elbow flexion/extension	V/V	V/V	Knee flexion/extension	III/III	III/III
Wrist extension	V	V	Ankle dorsiflexion/plantarflexion	I/I	I/I
Finger flexion/extension	V/V	V/V	Ankle inversion/eversion	I/I	I/I
Finger abduction	V	V	Big toe extension	I	I

Case Presentation

- ▶ **Physical examination (continue)**
 - **Sensory system:** decreased pinprick, pain and temperature below wrist and mid thigh both sides, impaired proprioception and joint vibration below wrist and knee both sides
 - DTR 1+ all except ankle reflexes 0 both
 - Babinsky's sign – negative
- ▶ **CBC: Hb 17.3 g/dL, Hct 49.5%, MCV 89 fL, WBC 18,460/cu.mm. (N81%, L16%, M2%), platelet 582,000/cu.mm.**

Case Presentation

- ▶ **Investigations**
- ▶ **Bone marrow aspiration and biopsy**
 - Hypocellular bone marrow (cellularity 20%)
 - No evidence of MPN, lymphoma, or granuloma
- ▶ **JAK2 V617F mutation:** negative
- ▶ **NCV:** Symmetrical sensory-motor polyneuropathy (primary demyelination with secondary axonopathy)
- ▶ **CSF profile:** WBC 0 cell/cu.mm., protein 97.3 mg/dl, glucose (CSF/serum) 66/88 mg/dl, culture: no growth

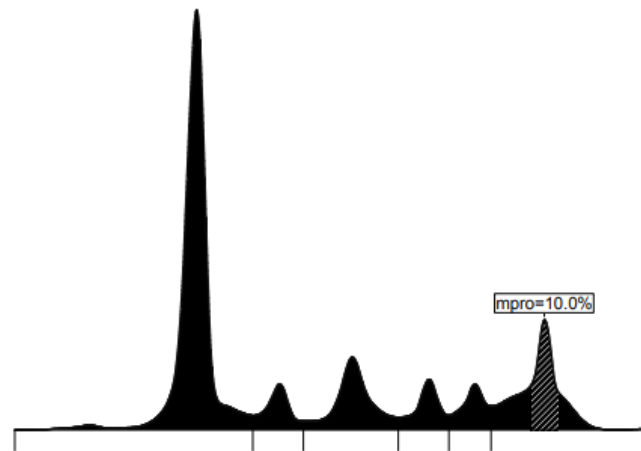
Case Presentation

▶ Investigations

▶ SPEP

Serum protein electrophoresis

Clin.Chem. Lab. Maharaj Nakorn CM Hospital



Sample barcode no: 1020075753

No: 9

Name :

HN :

Date: 07/08/2020

Fractions	%		Ref. %
Albumin	51.0	<	55.8 - 66.1
Alpha 1	5.7	>	2.9 - 4.9
Alpha 2	12.7	>	7.1 - 11.8
Beta 1	6.2		4.7 - 7.2
Beta 2	5.8		3.2 - 6.5
Gamma	18.6		11.1 - 18.8

Comments :

A/G : 1.04

(1.26 - 1.95)

▶ Serum free light chain (kappa/lambda) 20.7/70.1 mg/L

Case Presentation

- ▶ Investigations
- ▶ CT chest and abdomen

Results: The study shows

Chest:

- Subsegmental atelectases in bilateral basal lungs. Normal appearance of the remaining lung parenchyma without worrisome pulmonary nodule.
- No cardiomegaly or pericardial effusion.
- Several subcentimeter lymph nodes in mediastinum and both hilar regions, up to 1.0 cm in short axis.
- No significant axillary or supraclavicular lymphadenopathy.
- No pleural effusion.
- Homogeneous enhancement of both lobes of thyroid gland.

Abdomen:

- A 0.6-cm hypodense lesion in hepatic segment 5.
- Normal attenuation of the remaining liver parenchyma without focal lesion. The hepatic and portal veins are patent. No intrahepatic bile duct dilatation is detected.
- The gallbladder, spleen, pancreas, both adrenal glands and kidneys are normal.
- The opacified bowel loops are unremarkable. The urinary bladder is partially distended.
- Multiple small cysts in both ovaries, up to 0.8 cm in size.
- No ascites. No significant abdominal and inguinal lymphadenopathy.

Others:

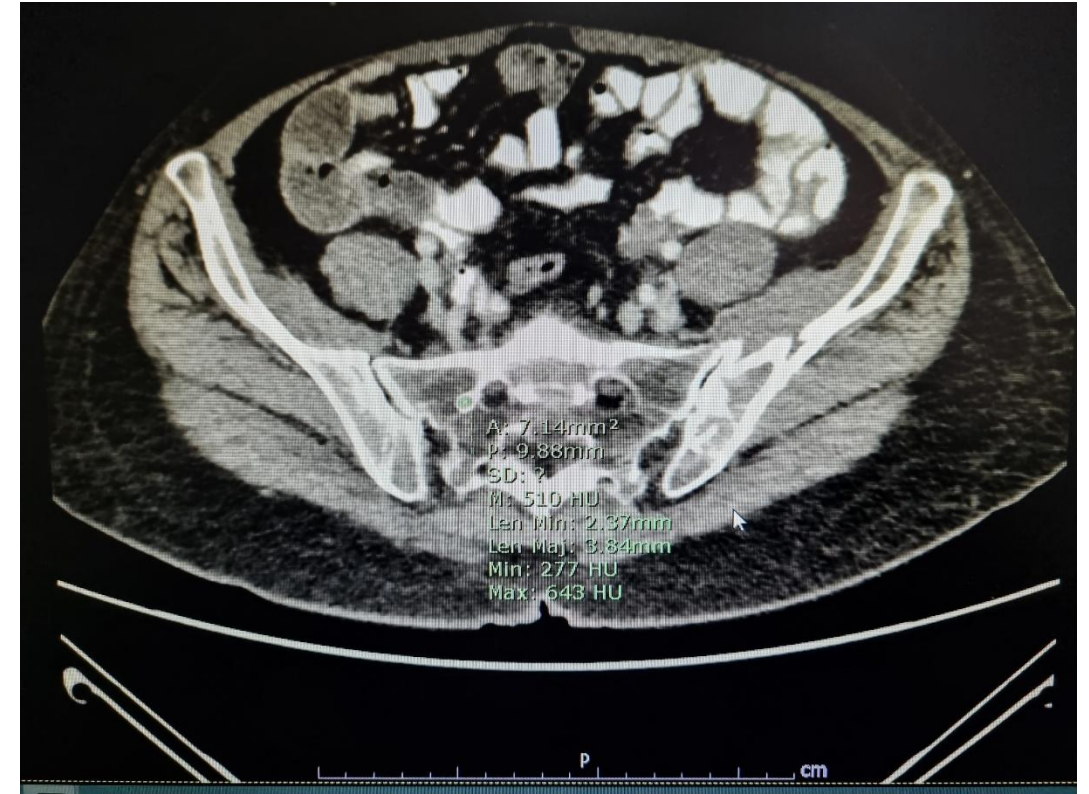
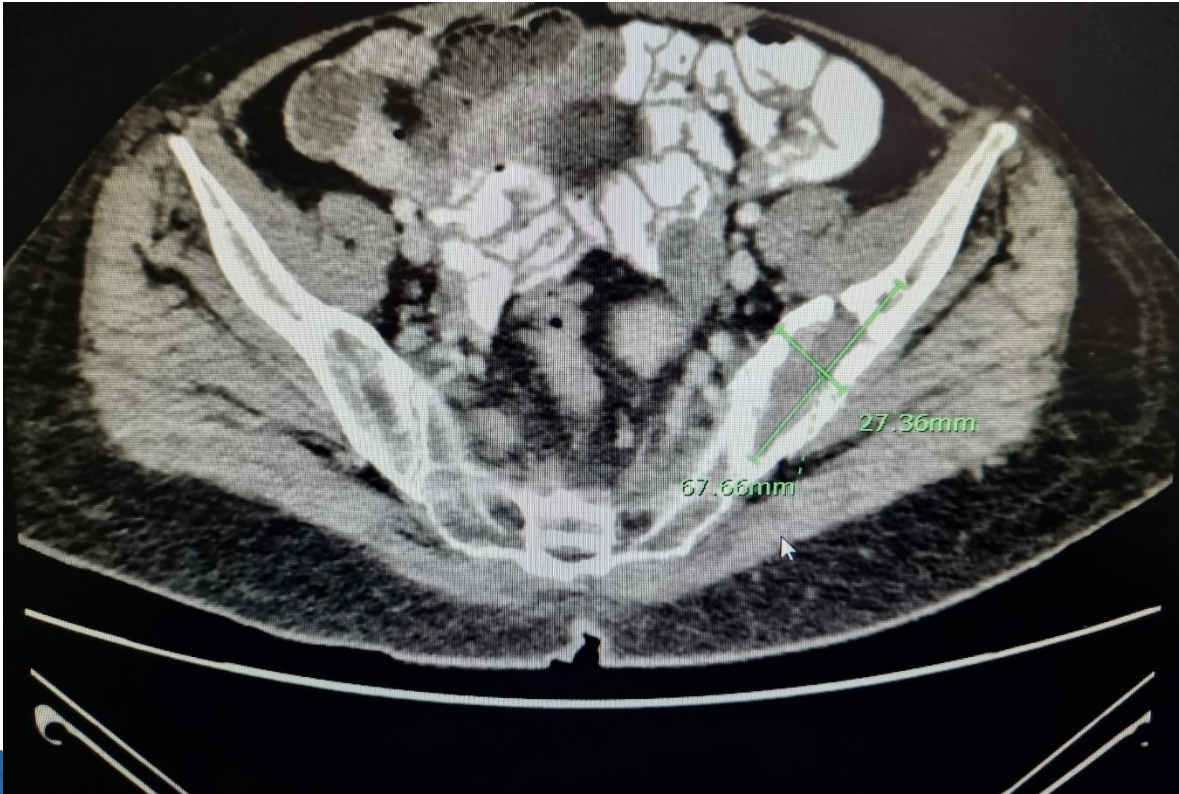
- As compared with the previous CT pelvic bone on 06/10/2020, there is no significant change of geographic expansile osteolytic lesion with internal septations and some cortical disruption in left iliac bone, measuring 2.7x6.6 cm in axial diameter.
- There is a 1.7-cm geographic osteolytic lesion in right sacral ala with sclerotic rim. Note associated right L5-S1 facet hypertrophy.
- A 0.7-cm osteosclerotic lesion in sacrum abutting right S1 sacral foramen, measuring 809 HU.
- Osteophyte formation with associated osteosclerotic change in superior L2, L4 and L5 vertebral end plates, possible degenerative change.
- A tract like lesion in right posterior iliac bone, likely post-procedural change.
- The remaining bony structure is intact.

IMPRESSION:

- A 2.7x6.6-cm rather aggressive bone tumor in left iliac bone. Ddx are plasmacytoma, giant cell tumor or desmoplastic fibroma. Tissue diagnosis is suggested.
- A 1.7-cm geographic osteolytic lesion in right sacral ala with sclerotic rim and associated right L5-S1 facet hypertrophy, favor benign bone lesion such as subchondral bone cyst or fibro-osseous lesion.
- A 0.7-cm osteosclerotic lesion in sacrum abutting right S1 sacral foramen, non-specific in nature but likely benign lesion.
- Osteophyte formation with associated osteosclerotic change in superior L2, L4 and L5 vertebral end plates, possible degenerative change.
- A 0.6-cm hypodense lesion in hepatic segment 5, non specific but possible cyst.

Case Presentation

- ▶ Investigations
- ▶ CT chest and abdomen



Case Presentation

- ▶ **Investigations**
- ▶ **Left iliac bone biopsy**
 - Monoclonal plasma cell neoplasm
 - CD138+ with lambda light chain restriction

POEMS Syndrome: Diagnosis

- ▶ Both mandatory criteria + One major criteria + One minor criteria

Mandatory major criteria	1. Polyneuropathy (typically demyelinating)
	2. Monoclonal plasma cell-proliferative disorder (almost always λ)
Other major criteria	3. Castleman disease ^a
(one required)	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 hemangiomas, 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

Case Presentation

▶ Investigations

▶ Left iliac bone biopsy

- Monoclonal plasma cell neoplasm
- CD138+ with lambda light chain restriction

▶ Diagnosis

- **Plasmacytoma with POEMS syndrome**
- **STEMI**

Outline

- ▶ **Monoclonal gammopathy with clinical significance (MGCS)**
- ▶ **Hematologic MGCS:**
 - Cold agglutinin disease (CAD)
 - Cryoglobulinemia
 - Monoclonal gammopathy with thrombotic significance (MGTS)
- ▶ **Monoclonal gammopathy of renal significance (MGRS)**
- ▶ **POEMS syndrome and neurologic MGCS**
- ▶ **TEMPI syndrome**
- ▶ **Cutaneous MGCS**

Outline

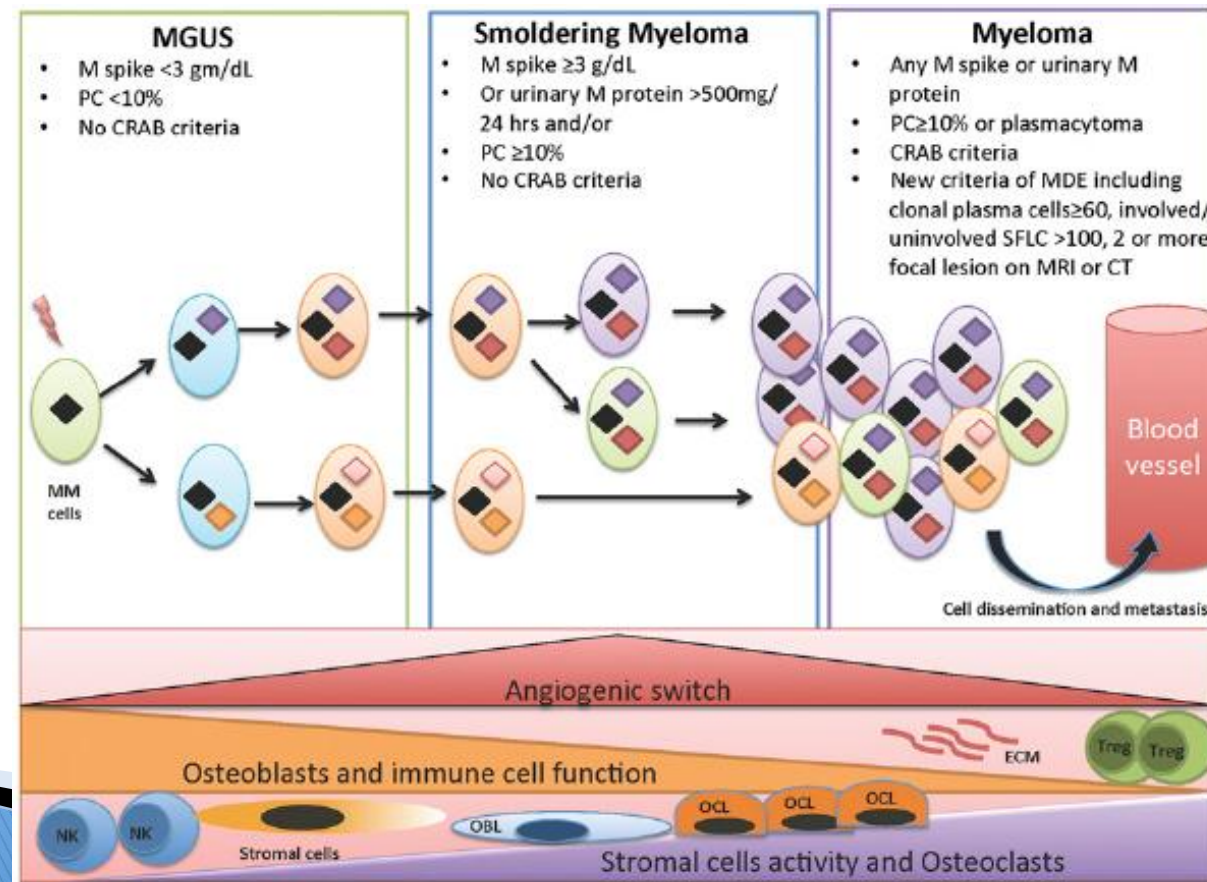
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- ▶ Cutaneous MGCS

Introduction

- ▶ **Monoclonal gammopathy**
- ▶ The presence in serum and/or urine of a monoclonal immunoglobulin (MIg) produced by abnormal B-cell clone
 - Plasma cells: IgG, IgA, IgD, or light chain
 - Lymphoplasmacytic cells: IgM

Introduction

- ▶ **MGUS: a benign condition with malignant potential and can associate with organ dysfunction**



Manifestations Associated with Monoclonal Gammopathies

- ▶ (1) Expansion of clonal malignant cells
- ▶ (2) Secretion of a large amount of Mlg
 - Hyperviscosity
 - LC cast nephropathy
- ▶ (3) Alterations of host immune system
 - Immune deficiency
 - Autoimmune manifestations
- ▶ (4) Pathogenic activities of Mlg or other mediators released by the clone

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- ▶ **(4) Pathogenic activities of Mlg or other mediators released by the clone**

Quiescent or small indolent B-cell clones
“MGCS”

Diseases Associated with MGUS

MGCS subtypes	Clinical features
Multi-organ syndromes	
- Cryoglobulinemia	Livedo reticularis, distal ischemia, neuropathy, glomerulonephritis, hyperviscosity, arthralgia
- POEMS	Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, sclerotic bone lesions and skin changes, anasarca, thrombocytosis, erythrocytosis
- Schnitzler syndrome	Urticaria, sclerotic bone lesions, constitutional symptoms
- TEMPI syndrome	Telangiectasia, elevated erythropoietin and erythrocytosis, monoclonal gammopathy, perinephric fluid collection, Intrapulmonary shunting

Diseases Associated with MGUS

MGCS subtypes	Clinical features
Hematologic MGCS	
- Cold agglutinin disease	Red cell agglutination, positive Coombs for C3, high cold agglutinin titer, thermal amplitude $\geq 30^{\circ}$ C
- Monoclonal gammopathy of thrombotic significance (MGTS)	Unexplained, recurrent thrombosis, positive for HIT testing without history of heparin exposure
- Acquired von Willebrand syndrome	Mucocutaneous bleeding
Renal MGCS (MGRS)	Nephritis, nephrotic syndrome, chronic kidney disease

Diseases Associated with MGUS

MGCS subtypes	Clinical features
Neurologic MGCS (MGNS)	
- IgM MGUS polyneuropathy	Polyneuropathy
- CANOMAD	Polyneuropathy, ophthalmoplegia, cold agglutinins
Cutaneous MGCS	
- Scleromyxedema	Generalized papular and sclerodermoid eruption Other signs: peripheral sensory and motor Neuropathy, carpal tunnel syndrome, dermatoneuro syndrome, dysphagia, scleroderma-like renal crisis
- Scleredema	Sclerotic skin disease, non-pitting induration of the skin, ulcers
- Necrobiotic xanthogranuloma	Cutaneous papules, plaques, and/or nodules, most often yellow or orange (periorbital skin is most common site)

Pathophysiological Classification of MGCS-related Disorders

- ▶ **Tissue deposition of all or part of MIg**
 - Monoclonal gammopathy of renal significance (MGRS)
- ▶ **Autoantibody activity**
 - Cold agglutinin disease (CAD)
- ▶ **Complement alternative pathway (CAP) activation**
- ▶ **Cytokine mediated**
 - POEMS syndrome
- ▶ **Unknown mechanism**
 - TEMPI syndrome

Pathophysiological Classification of MGCS-related Disorders

	Mechanism	Main MIg	Main organ(s) involved
Autoantibody activity			
Type II mixed cryoglobulinemia	Rheumatoid	IgM	Immune complex–mediated vasculitis; skin +++, kidney, peripheral nerve; may be systemic
C1 inhibitor deficiency	C1 inhibitor		Angioedema
Von Willebrand disease	vW factor		Bleeding
Bullous skin diseases	DE junction (collagen VII)		Skin
Xanthomatosis	Various lipoproteins	Usually IgG	Cholesterol accumulation in macrophages; skin and tendons; other localizations (necrobiotic xanthogranulomatosis)
Cold agglutinin disease	Red blood cell (Ii)	IgM	Cold-induced skin manifestations + intravascular hemolysis
IgM-associated peripheral neuropathy	MAG +++ Gangliosides	IgM	Peripheral nerve; ataxic polyneuropathy (anti-MAG) CANOMAD

CANOMAD, chronic ataxic neuropathy, ophthalmoplegia, monoclonal IgM protein, cold agglutinins, anti-disialosyl antibodies

Pathophysiological Classification of MGCS-related Disorders

	Mechanism	Main MIg	Main organ(s) involved
Complement alternative pathway (CAP) activation			
C3 glomerulonephritis	Mechanism to be determined; autoantibody activity against CAP regulator protein (factor H) in some cases	IgG	Kidney only
Atypical hemolytic uremic syndrome			Systemic
Cytokine mediated			
POEMS syndrome	VEGF	λ LC (100%), IgA (50%), V λ 1 (100%)	Peripheral nerve (100%), osteosclerotic bone lesions, and various other Manifestations

POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
 TEMPI, telangiectasias, erythrocytosis with elevated erythropoietin level, monoclonal gammopathy, perinephric fluid collection, and intrapulmonary shunting

Pathophysiological Classification of MGCS-related Disorders

	Mechanism	Main Mlg	Main organ(s) involved
Unknown mechanism			
Systemic capillary leak syndrome		IgG, IgA (rare)	Systemic
TEMPI syndrome		IgG	Systemic
Neutrophilic dermatosis		IgA 80% (except Sweet)	Skin +++; different types and different associated manifestations
Acquired cutis laxa		Usually IgG; association with γ HCDD	Skin +++, Other manifestations (lung, digestive tract)
Scleromyxedema		IgG with slow electrophoretic mobility	Skin +++; other localizations
Schnitzler syndrome	Autoinflammatory syndrome by IL-1 deregulation?	IgM	Skin +++; systemic symptoms; osteosclerotic bone lesions
Sporadic late-onset nemaline myopathy			Exclusively muscles (skeletal and possibly cardiac)

Diagnosis of MGCS

- ▶ **Pathological demonstration of Mlg deposition in the affected tissue or organ**
 - Immunohistological techniques
 - Electron microscopy
 - Mass spectrometry
- ▶ **Mlg-mediated immune process**
 - High titer of autoantibody activity
- ▶ **Other mechanism**
 - Complement level
 - Epidemiological data and presence of Mlg

Management of MGCS

- ▶ **Indication for therapy is driven by organ damage due to the secreting clone**
- ▶ **Benefit-to-risk approach**
- ▶ **Anti-B-cell/plasma cell agents**
 - Chemotherapy
 - Novel agents including monoclonal antibody
- ▶ **Other options**
 - Local irradiation
 - High-dose IV immunoglobulins: autoantibodies

Outline

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Cold agglutinin disease (CAD)

- ▶ **Autoimmune hemolytic anemia mediated by monoclonal cold agglutinins**
 - Driven by an underlying clonal B-cell lymphoid proliferation
 - Not fulfilling criteria for a B-cell lymphoma
- ▶ **Rare disease**
 - The estimated annual incidence 1–1.8 per million
 - Its prevalence is four-fold higher in colder countries

	Population, 10 ⁶	Prevalence, cases/10 ⁶ inhabitants	Incidence, cases/10 ⁶ inhabitants/y	Outdoor temperature, °C, yearly-average
Norway	5.32	20.5	1.9	6.0*
Lombardy, Italy	7.0†	5.0	0.48	13.1

CAD: Multinational Study

► Clinical phenotypes

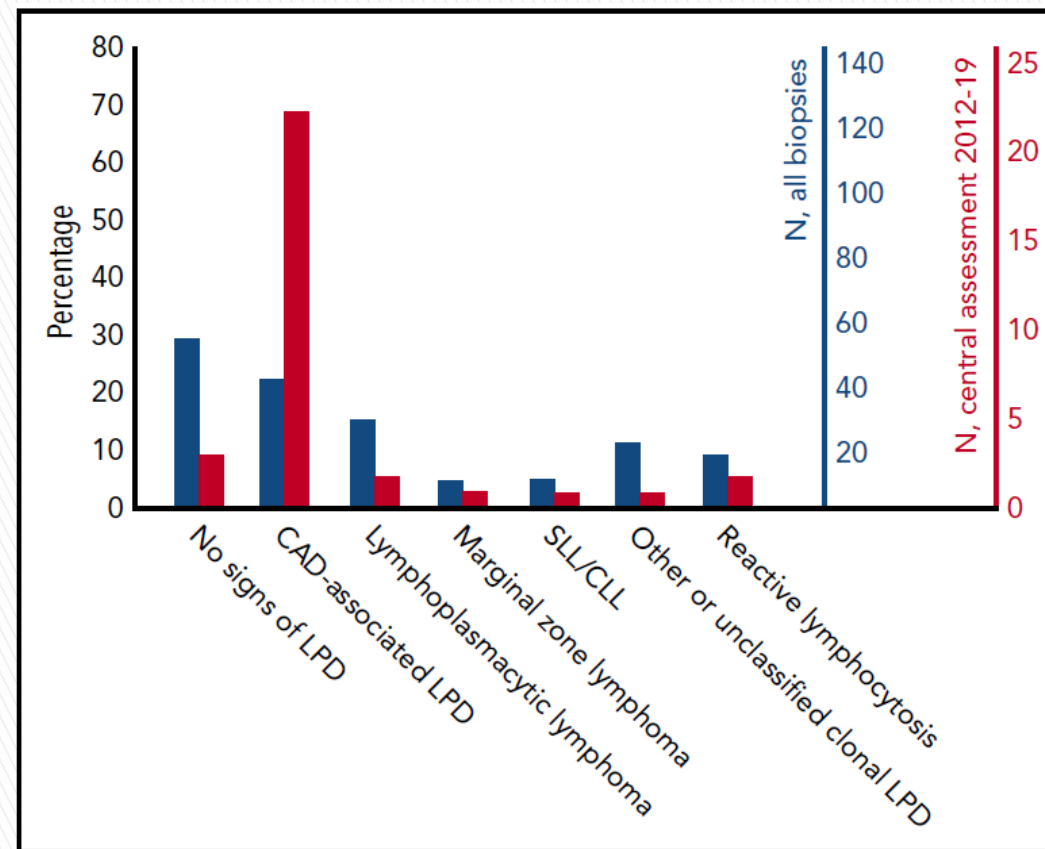
Clinical phenotype		Frequency	
Type	Definition	n	%
1	Hemolytic anemia with circulatory symptoms grade 1 or absent	146	69.5
2	Hemolytic anemia with circulatory symptoms grade 2-3	44	21.0
3	Circulatory symptoms with compensated hemolysis	20	9.5
All patients with available data		210	100.0

Circulatory symptoms grade 1, acrocyanosis only; grade 2, Raynaud-like symptoms interfering with daily living; grade 3, gangrene or ulcerations.

CAD: Multinational Study

	Median (range)	Within reference range, % of patients
Hemoglobin, g/dL	9.2 (4.5-15.3)	10.0
Total bilirubin, $\mu\text{mol/L}$	36 (5-136)	14.3
Lactate dehydrogenase, U/L	380 (117-2026)	9.7
Haptoglobin, g/L	<0.1 (<0.1-9.0)	11.2
Reticulocytes, 10^9 cells/L	147 (13-778)	20.7
Total IgM, g/L	3.2 (0.2-74)	34.6
Cold agglutinin titer at 4°C	512 (16-819,200)	8.6

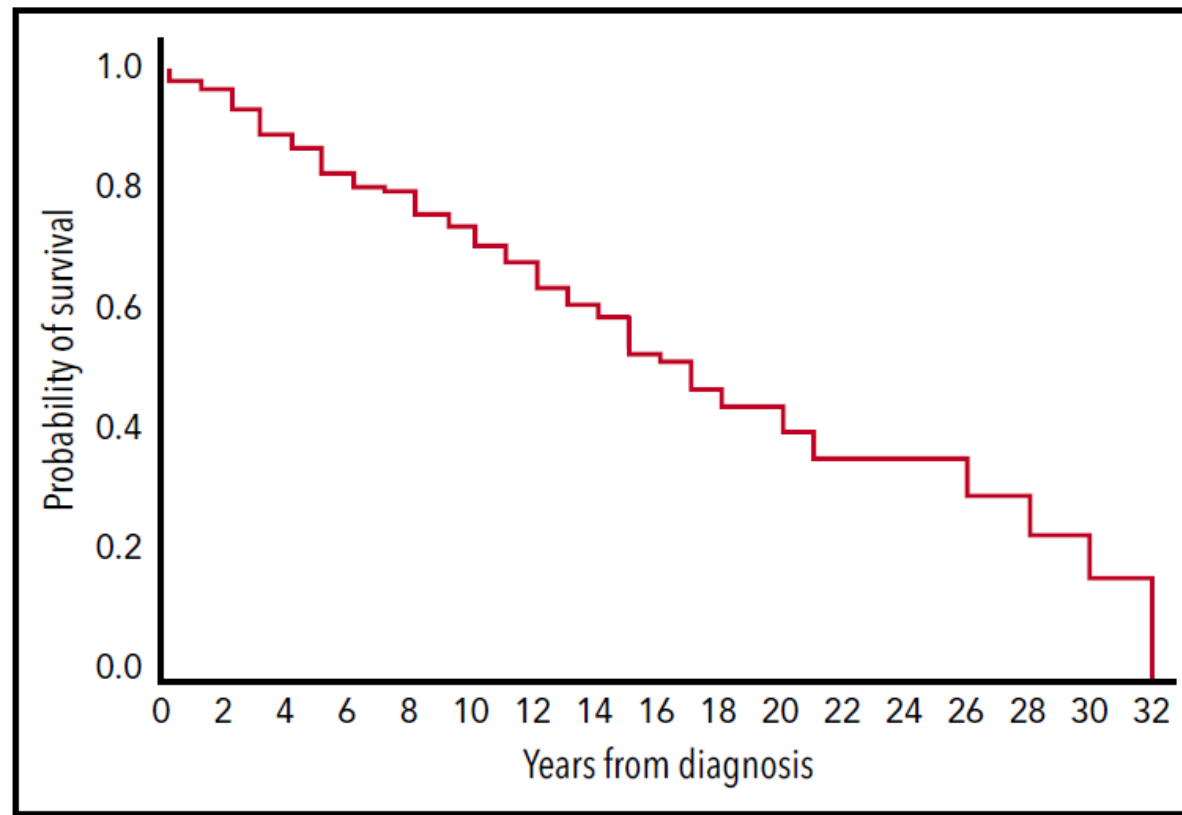
Laboratory findings



Bone marrow biopsy

CAD: Multinational Study

► Survival outcomes



5-year OS 83%
(3.5% CAD-related death)

Thromboembolic events 12.9%
(arterial 63%)

Treatment of CAD

► Rituximab-based therapy

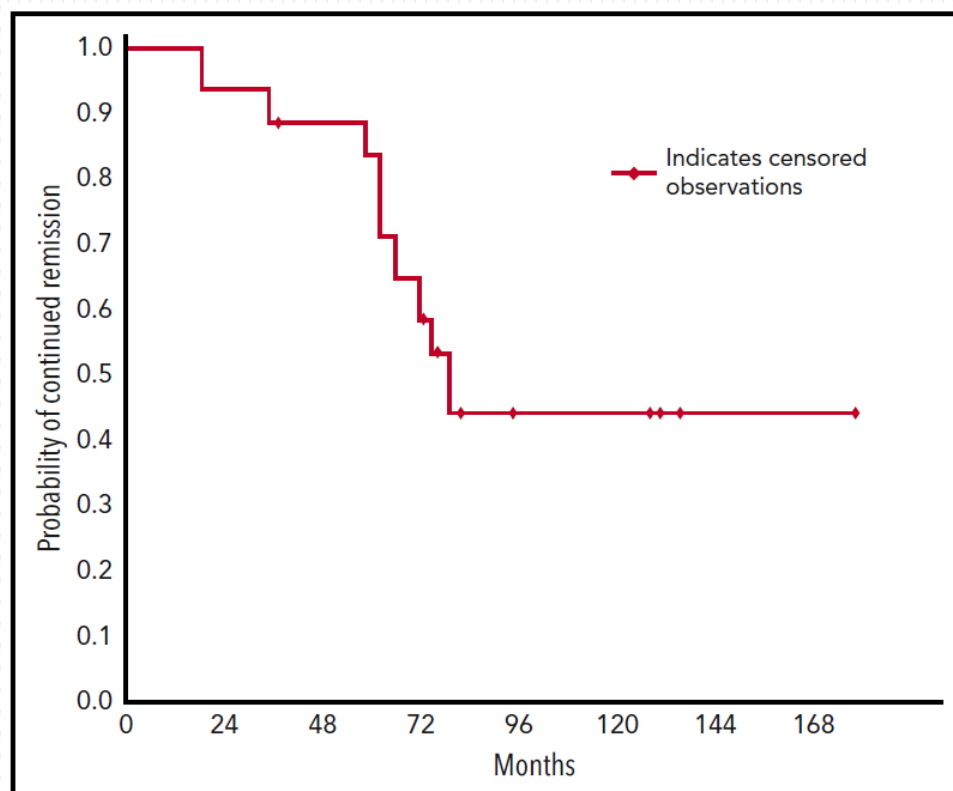
Regimen	N	Response rate	Median duration of response	Adverse events
Rituximab monotherapy ¹	27	54% (95% PR)	11 months	
Rituximab-fludarabine ²	29	76% (CR 21%)	> 6.6 months	Grade 3-4 hematologic 41% Grade 1-3 infection 59%
Rituximab-bendamustine ³	45	71% (CR 40%)	32 months	Grade 3-4 neutropenia 33% Infection 11%

1 Berentsen S. Blood 2004; 103:2925–8.

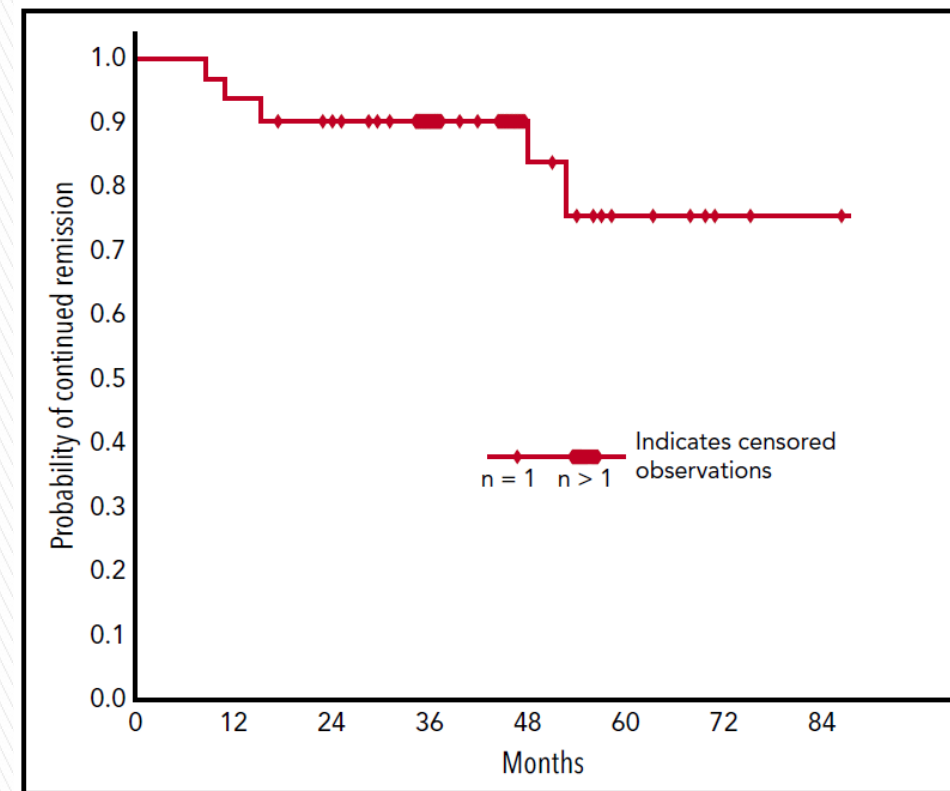
2 Berentsen S. Blood 2010;116:3180–4.

3 Berentsen S. Blood 2017;130:537–41.

CAD: Multinational Study

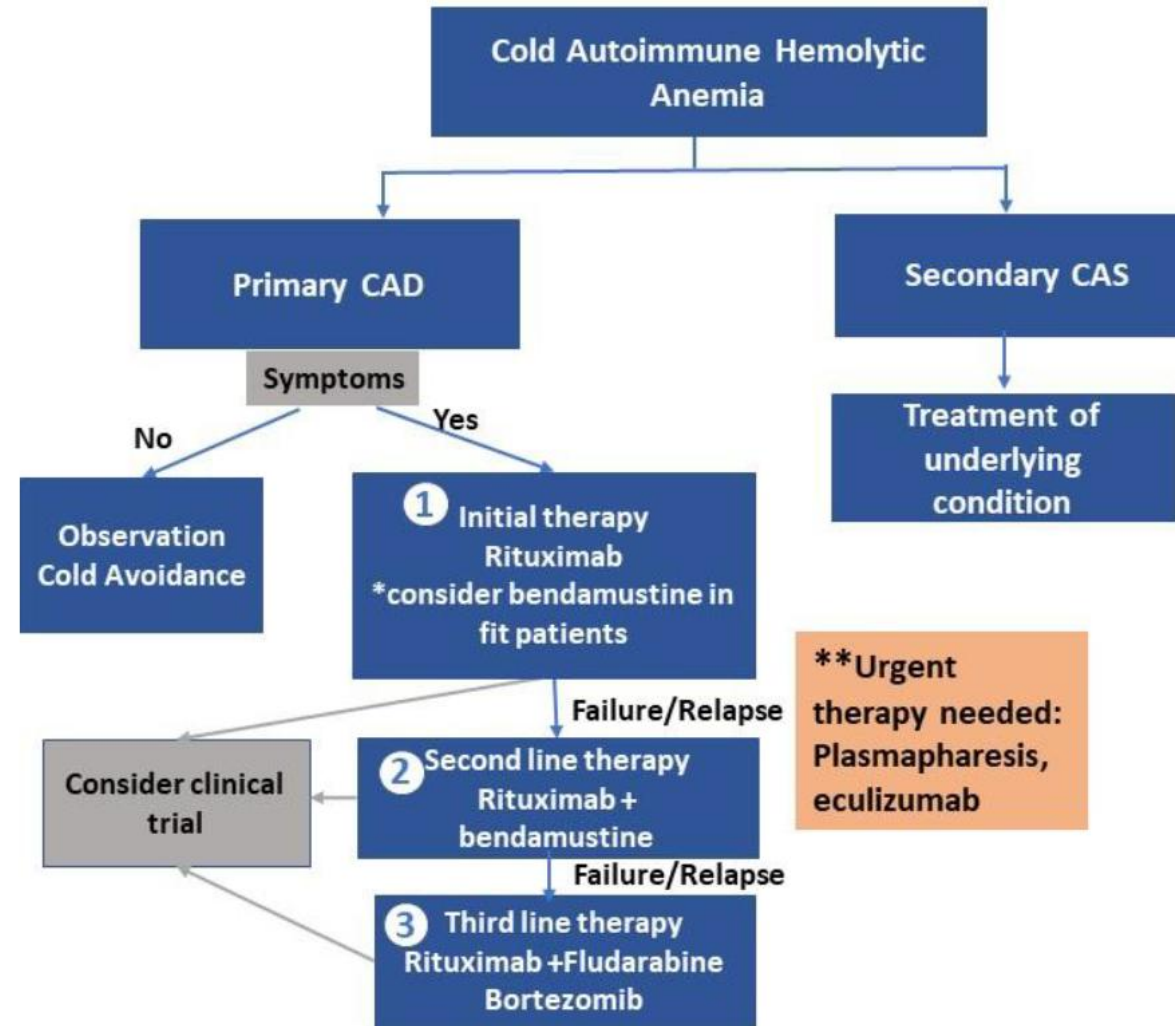


Rituximab-fludarabine



Rituximab-bendamustine

Treatment of CAD



Treatment of CAD

► Novel agents

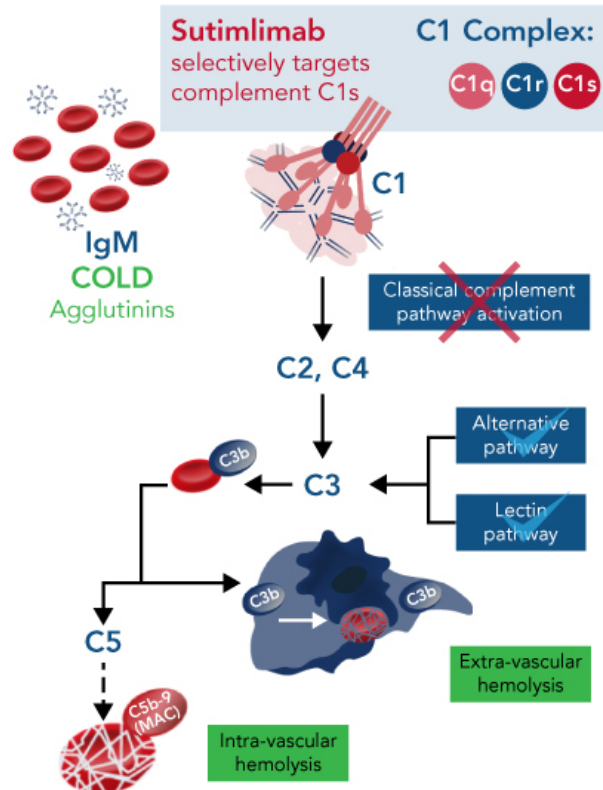
Regimen	N	Response rate	Duration of response	Adverse events
Bortezomib ¹ (Relapsed/refractory)	19	32% (CR 16%)	66% at median F/U 16 months	Grade 3-4 AEs 31.6%
Ibrutinib ² (12 Relapsed/refractory)	13	100% (CR 92%)	100% at median F/U 12 months	Grade 3 neutropenia 7.7%
Eculizumab ³ (7 Relapsed/refractory)	13	8/9 transfusion independent	NA	Severe AEs in 2 patients (1 SBP, 1 pneumonitis)
Sutimlimab ⁴	7	7/7 transfusion independent	NA	Serious AE in 1 patients (post-operative bleeding not related to study drug)

1 Rossi G. Blood 2018;132:547–50. 2 Jalink M. Blood 2021;138:2002-5.

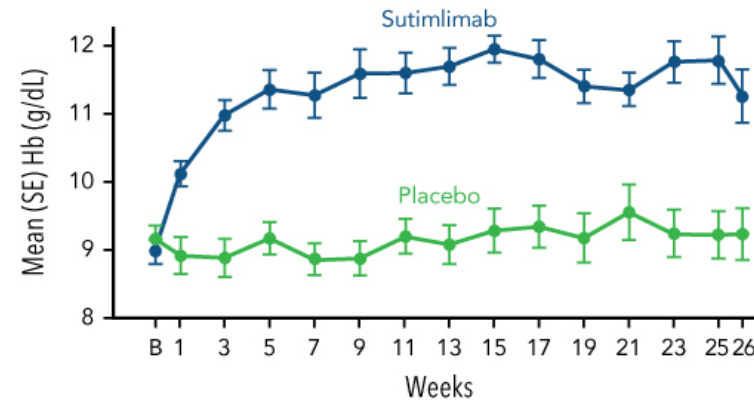
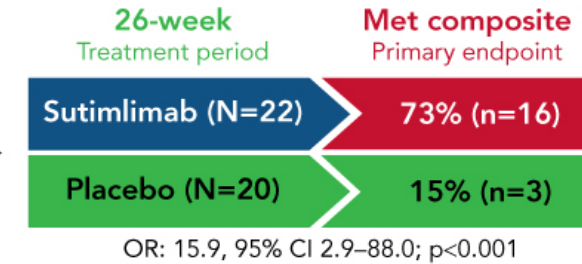
3 Röth A. Blood Adv 2018;2:2543–9. 4 Gelbenegger G. Blood Adv 2020;4:997–1005.

Sutimlimab in CAD: CADENZA

Sutimlimab in patients with cold agglutinin disease (CAD):
Randomized placebo-controlled phase 3 cadenza trial (NCT03347422)



Patient with
CAD
(No recent history
of RBC transfusion)



Early and sustained
Effects of sutimlimab on:

- ✓ Anemia
- ✓ Hemolysis
- ✓ Fatigue

No meaningful changes
observed with placebo

CI, confidence interval; Hb, hemoglobin; IgM, immunoglobulin M; MAC, membrane attack complex; OR, odds ratio; RBC, red blood cells; SE, standard error

Alexander Röth et al. *Blood*

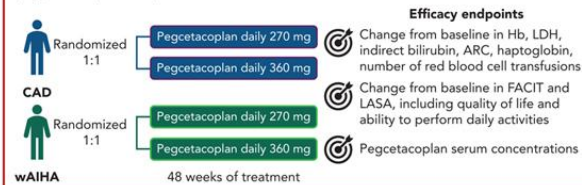
Sutimlimab treatment was effective and generally well tolerated. Results from CADENZA demonstrate that sutimlimab has the potential to be an important advancement in the treatment of hemolysis in CAD.

Pegcetacoplan in CAD

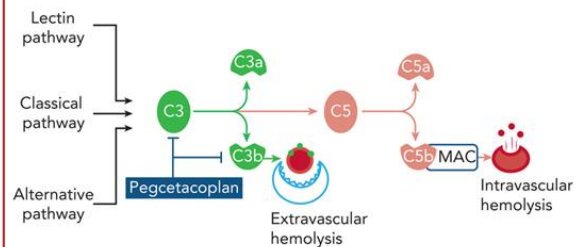
A Phase 2 Study of Pegcetacoplan in Patients With Cold Agglutinin Disease (CAD) and in Patients with Warm Antibody Autoimmune Hemolytic Anemia (wAIHA)

Background

PLAUDIT study: to assess the safety, efficacy and PK of pegcetacoplan in patients with CAD or wAIHA



Mode of action of pegcetacoplan



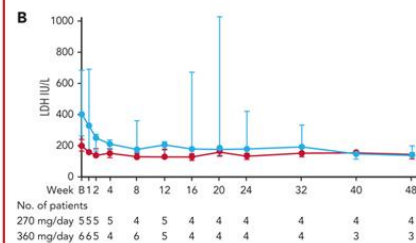
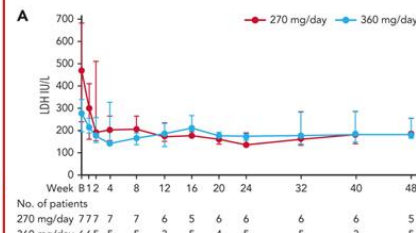
Conclusions: Pegcetacoplan was well tolerated and increased hemoglobin levels, reduced hemolysis, and increased FACIT-fatigue scale scores in patients with CAD and wAIHA.

Roman et al. DOI: 10.1182/*blood*.2023022549



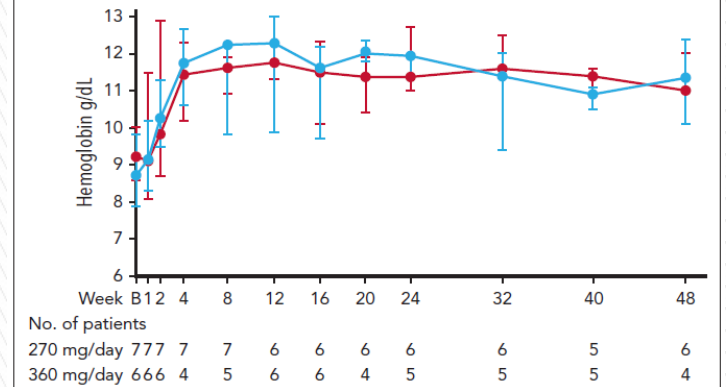
Key outcomes

Median (interquartile range) LDH levels over 48 weeks in patients with CAD (A) and wAIHA (B)

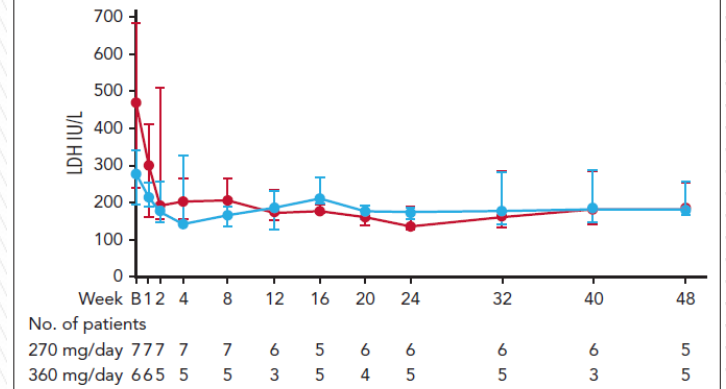


ARC, absolute reticulocyte count; CAD, cold agglutinin disease; FACIT, Functional Assessment of Chronic Illness Therapy - Fatigue scale; hb, hemoglobin; LASA, linear analogue self-assessment; LDH, lactate dehydrogenase; MAC, membrane attack complex; PK, pharmacokinetics; Q2W, twice weekly; wAIHA, warm antibody autoimmune hemolytic anemia

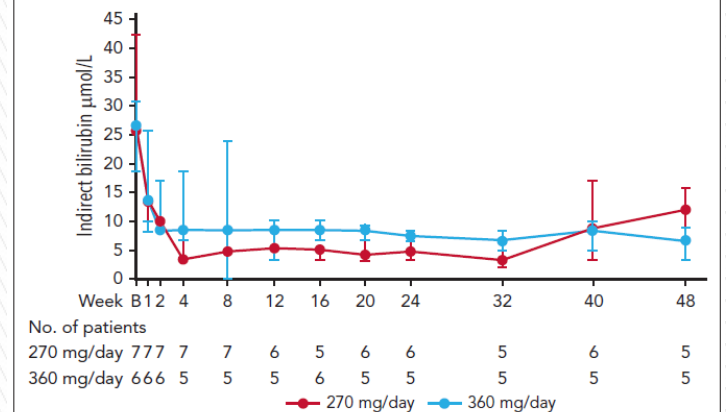
A



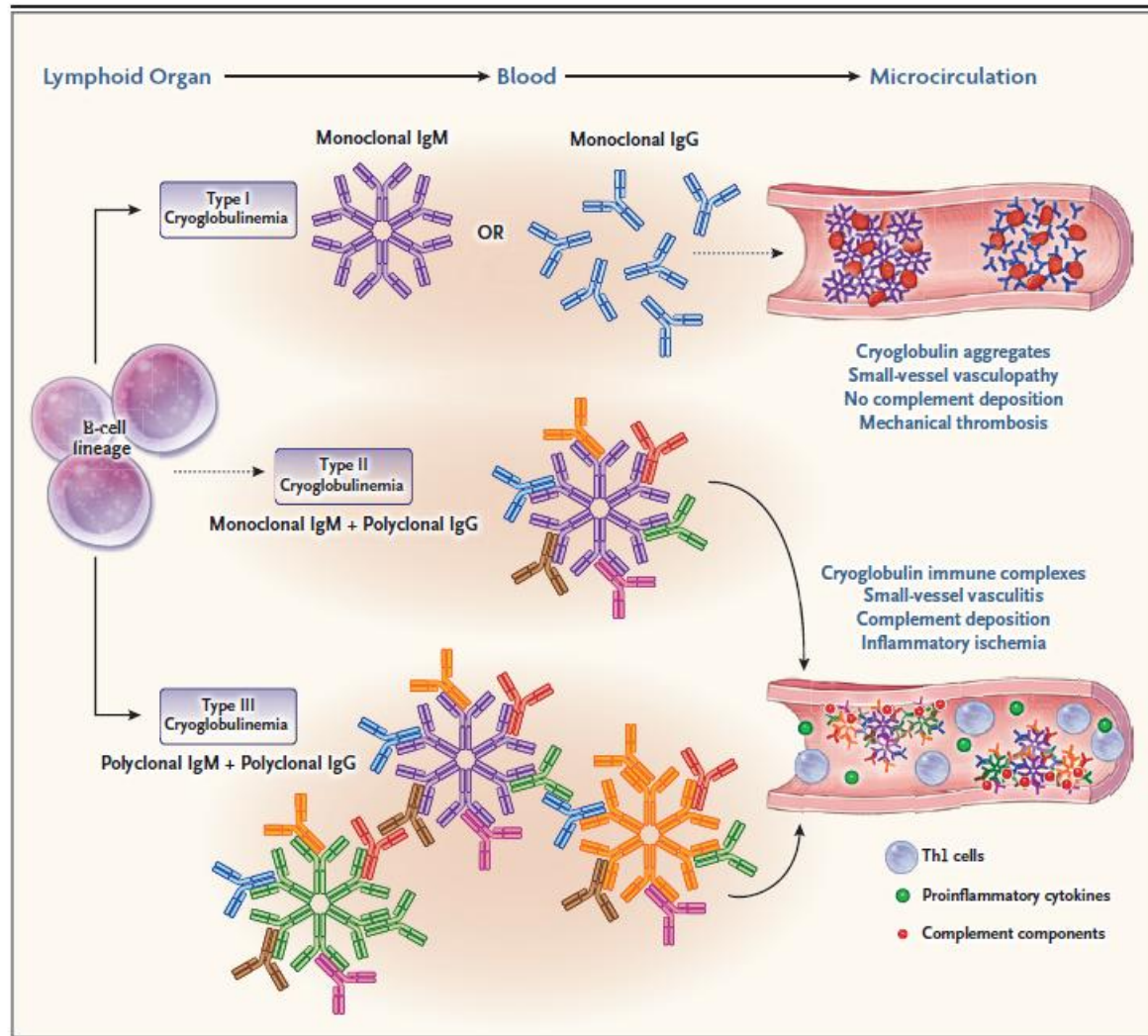
B



C



Cryoglobulinemia

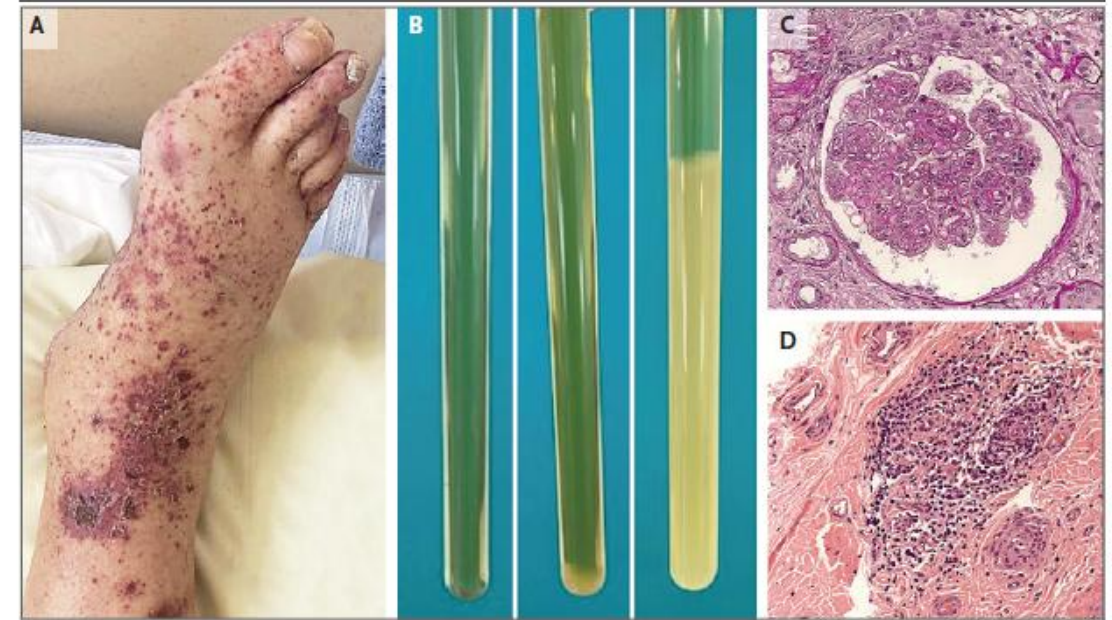
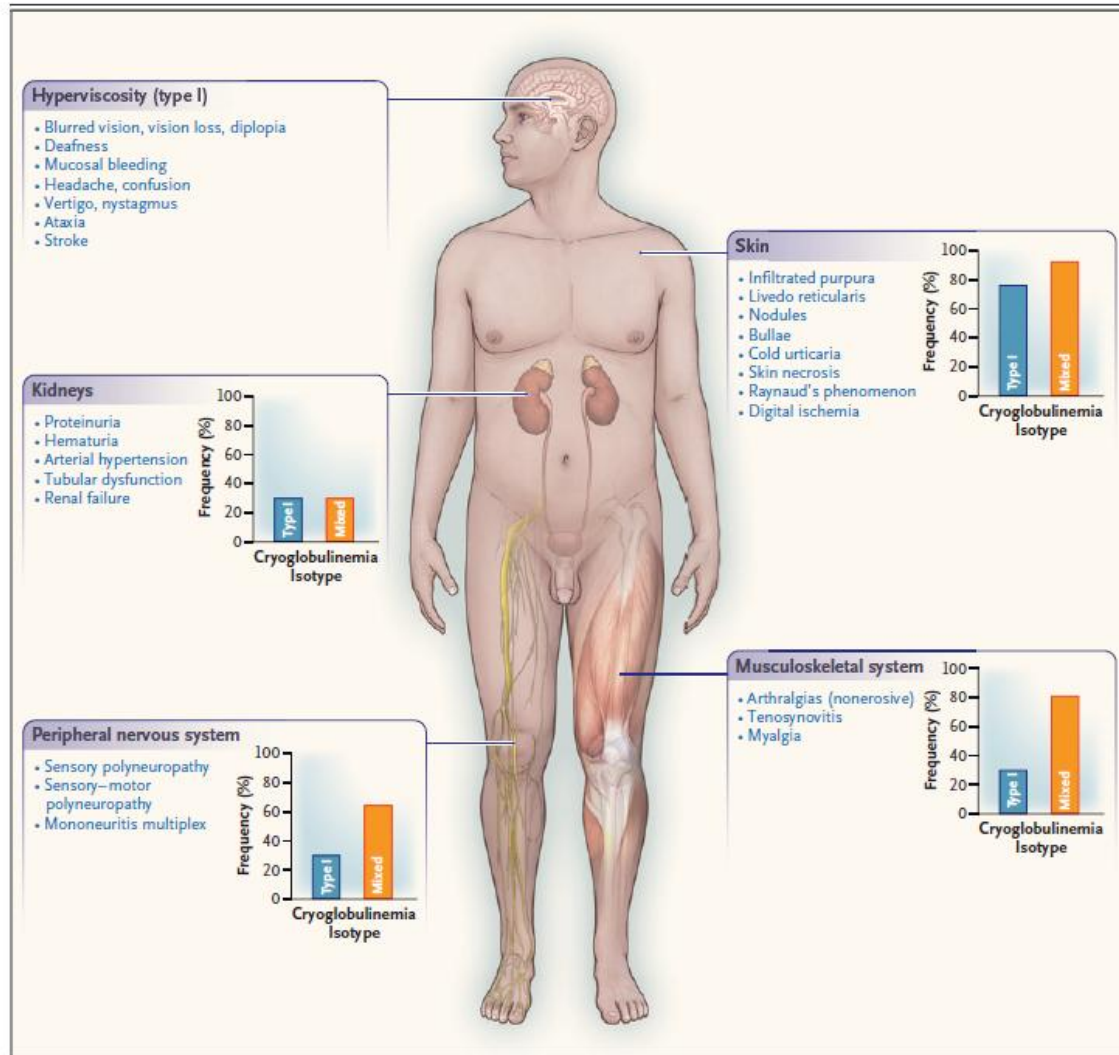


- **Precipitation of circulating immunoglobulins from human serum when cooled below 4°C**

Table 1. Main Causes of Cryoglobulinemia.*

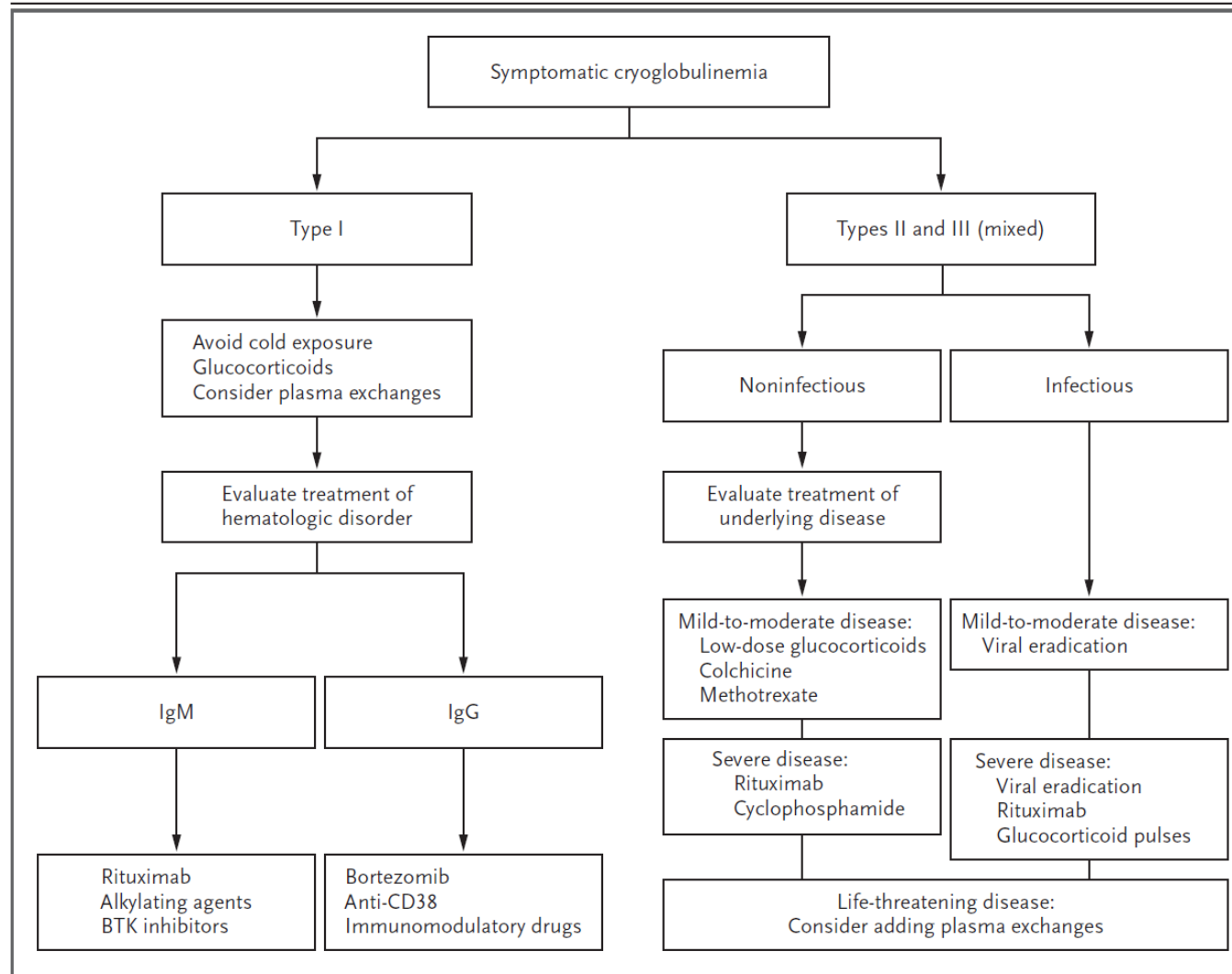
Cause	Disorders
Hematologic disorders	Waldenström's macroglobulinemia Multiple myeloma Non-Hodgkin's lymphoma Chronic lymphocytic leukemia Monoclonal gammopathy of clinical significance
Systemic autoimmune diseases	Sjögren's syndrome Systemic lupus erythematosus Rheumatoid arthritis
Chronic viral infections	Hepatitis C Hepatitis B Human immunodeficiency virus
Others (very rare)	Viral infections (e.g., adenovirus, herpes viruses, Epstein-Barr virus, varicella-zoster virus, human T-cell leukemia virus type 1, influenza virus, parvovirus B19, rubella virus) Bacterial infections (e.g., brucella, infective endocarditis, Lyme disease, rickettsia, syphilis) Fungal infections (e.g., coccidioidomycosis) Parasitic infections (e.g., echinococcosis, leishmaniasis, malaria, schistosomiasis, toxoplasmosis, trypanosomiasis)

Cryoglobulinemia: Clinical Manifestations



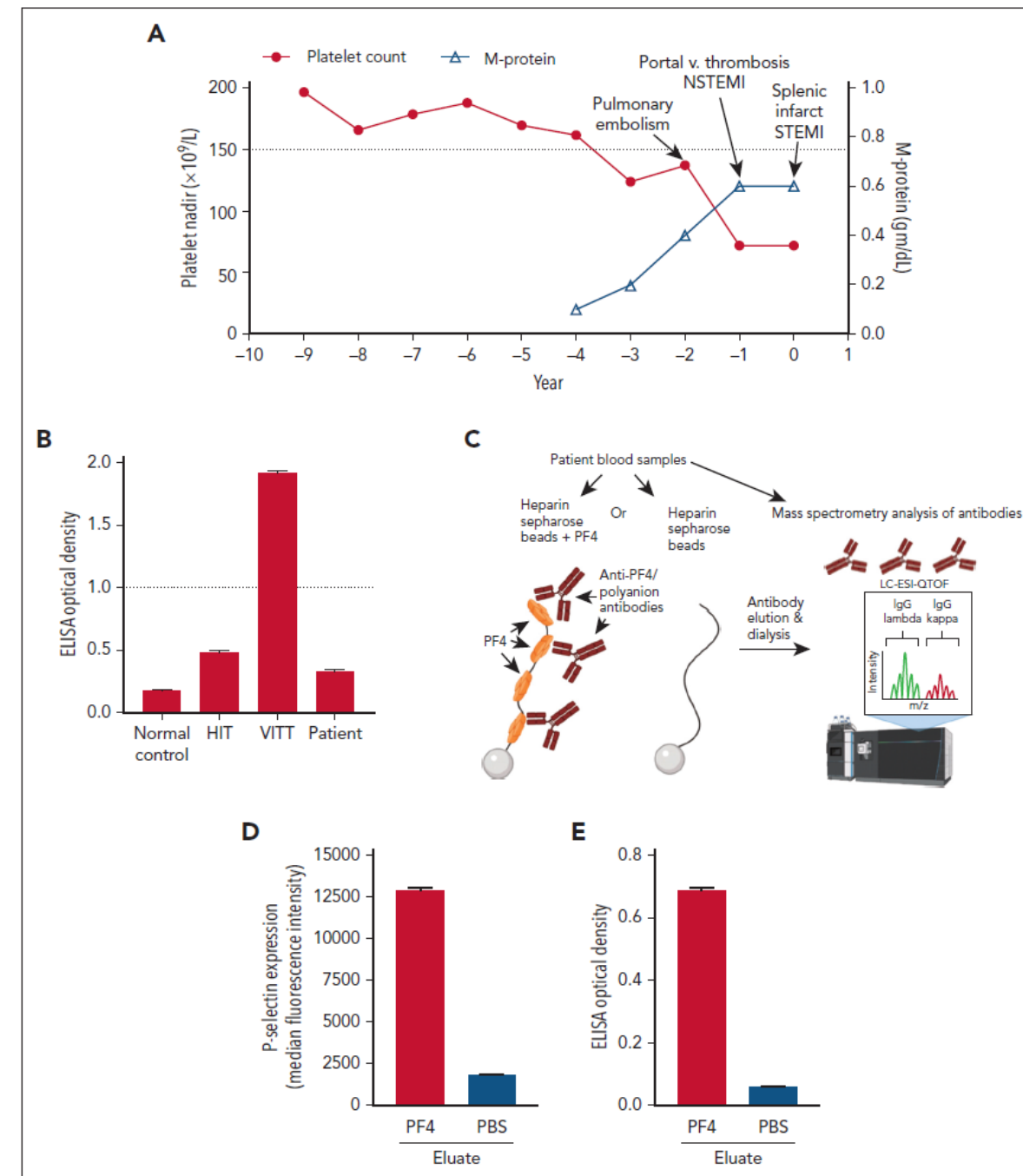
- A. Vascular purpura of the lower limbs
- B. Detection of cold-induced precipitates (cryoglobulin)
- C. Renal biopsy shows type I membranoproliferative glomerulonephritis
- D. Peripheral-nerve biopsy shows a perivascular lymphocytic infiltrate adjacent to affected nerves

Cryoglobulinemia: Management



MGTS

- ▶ Recurrent thrombosis and thrombocytopenia
- ▶ Secondary to persistent anti-PF4/polyanion monoclonal antibody
- ▶ “VITT-like” antibody
- ▶ Underlying neoplastic condition

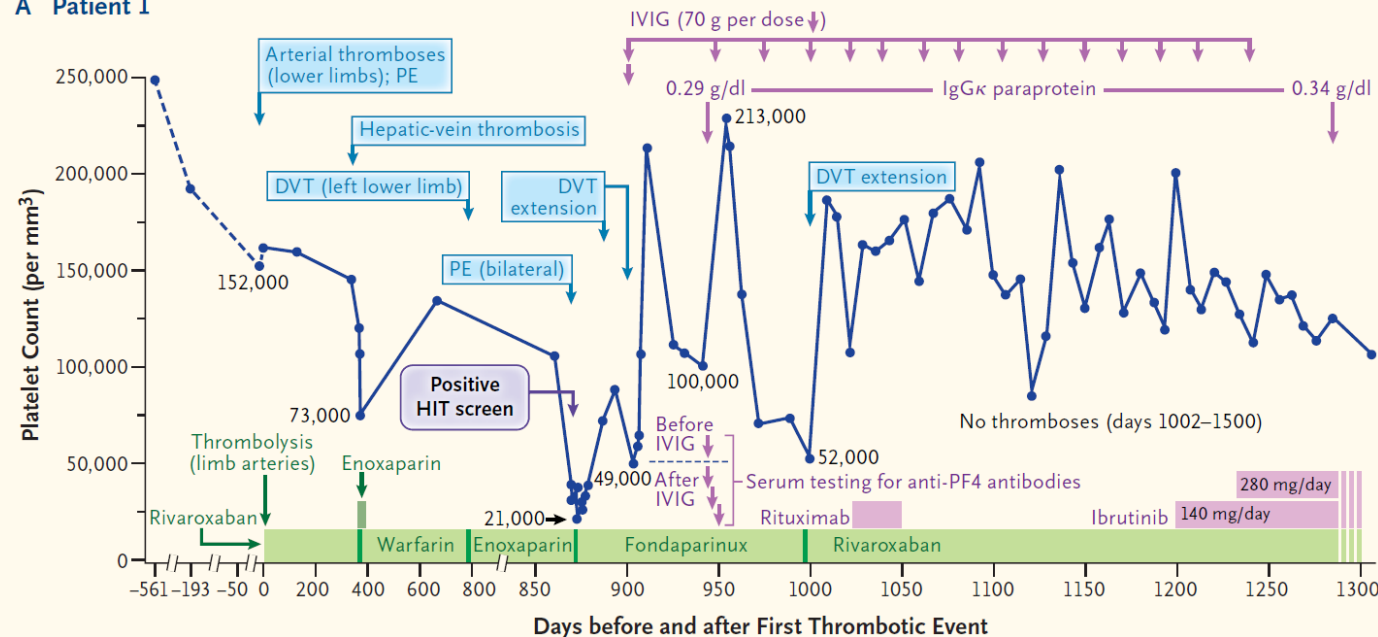


VITT-Like MGTS: Disease Course

- May not necessarily have chronic thrombocytopenia

- Thrombocytopenia exacerbation often occurs in association with thrombotic events

A Patient 1



B Patient 2

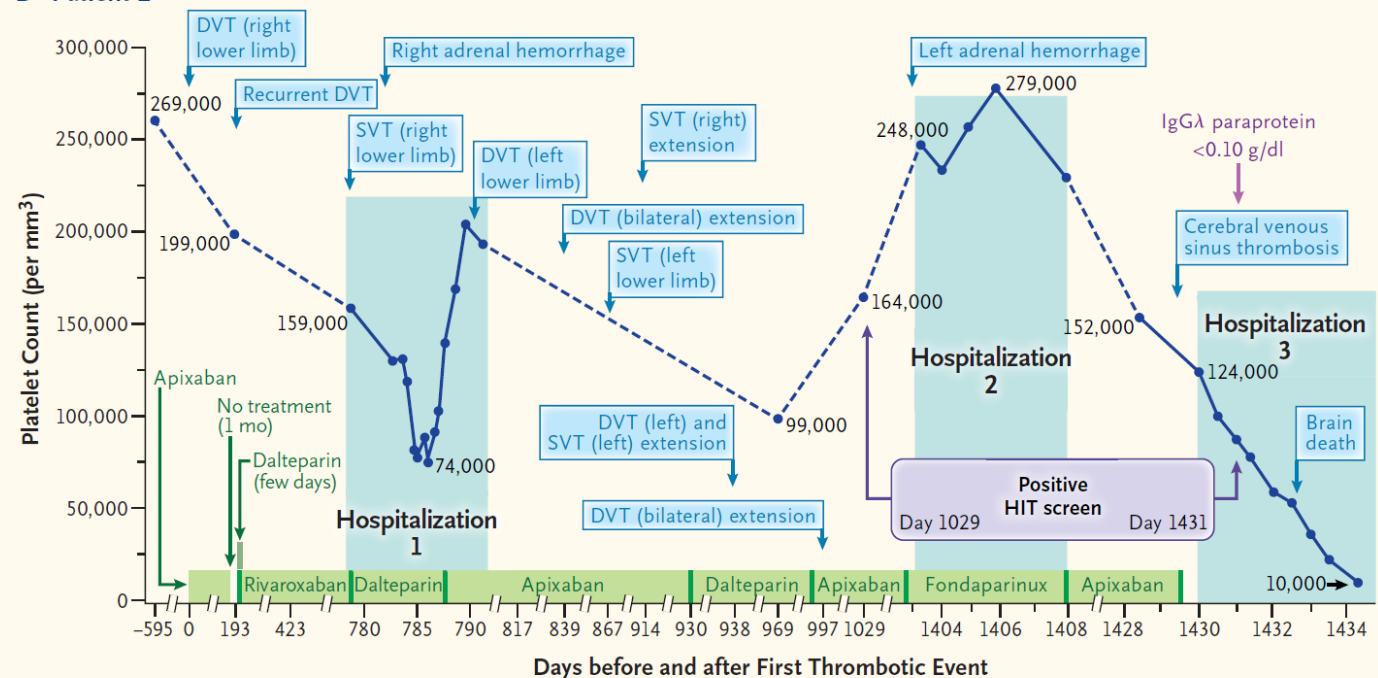
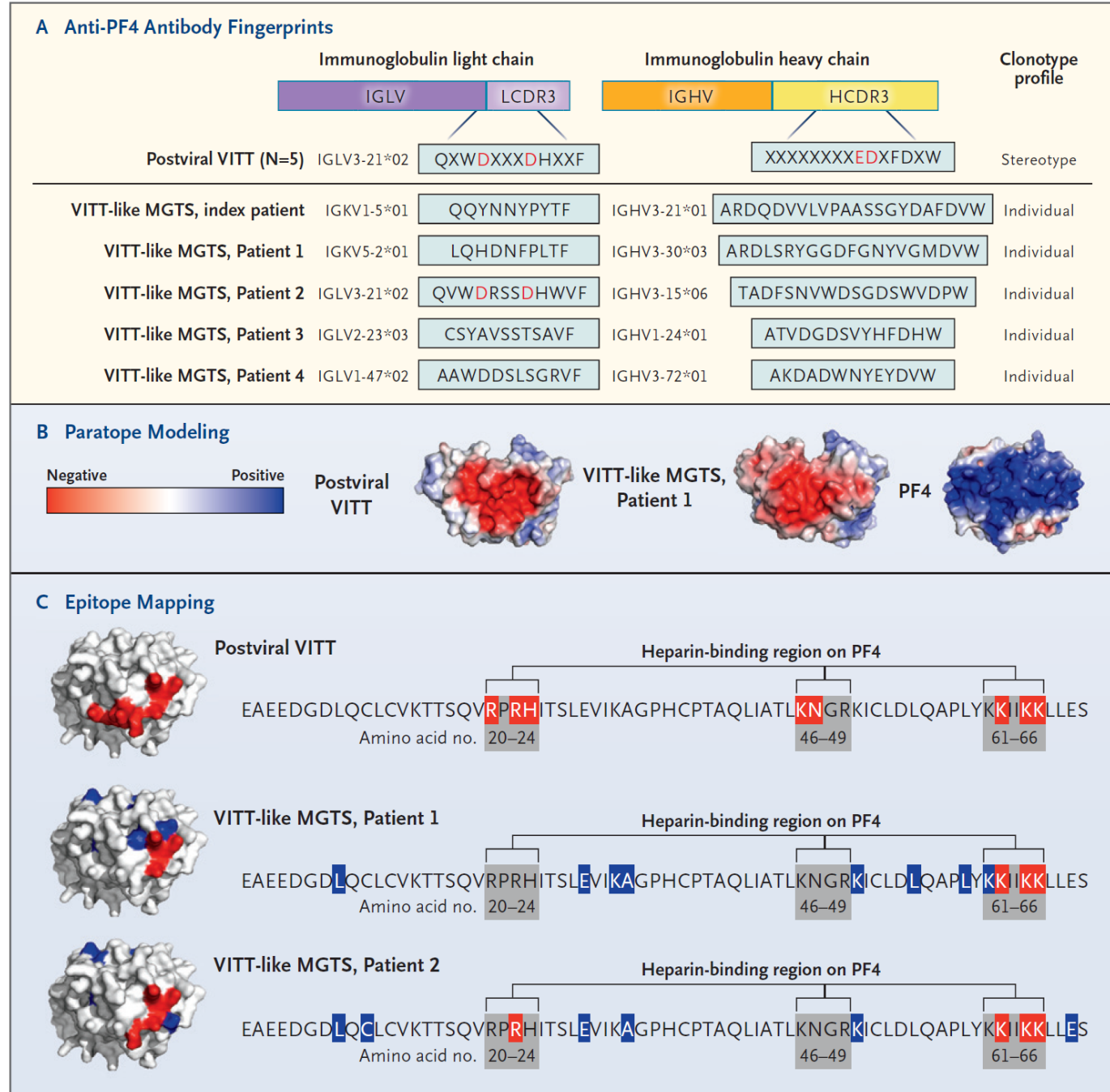
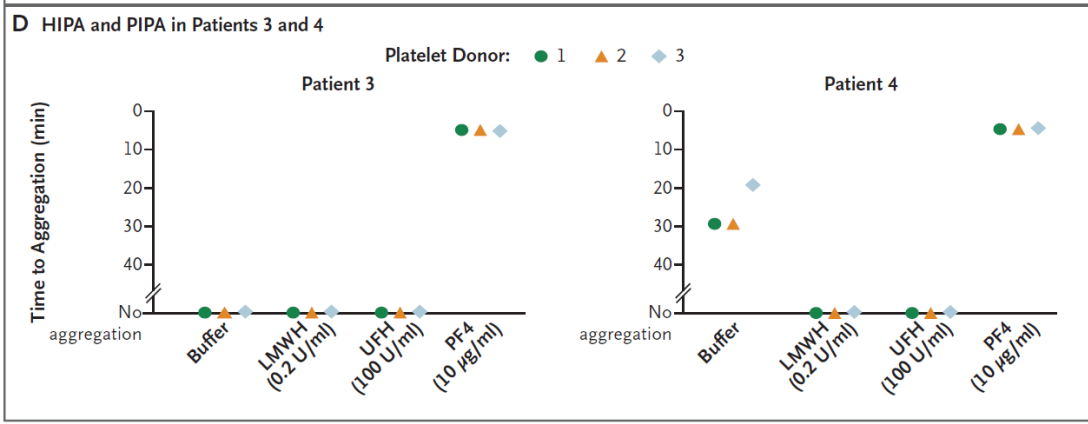
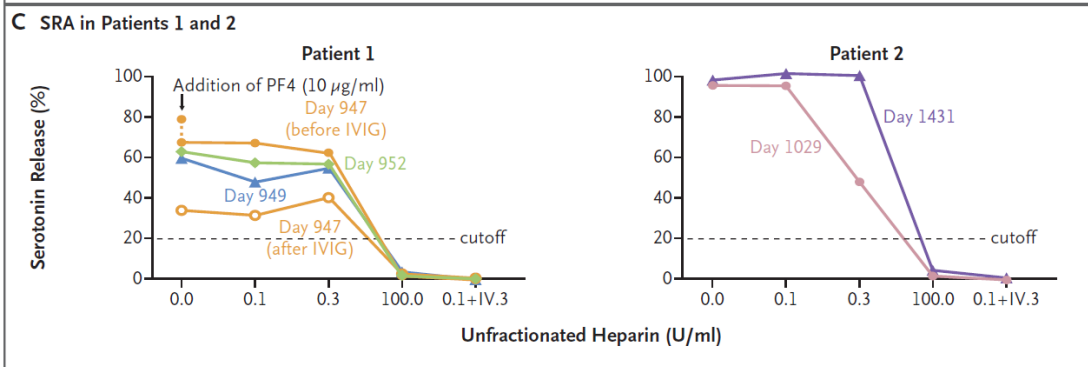
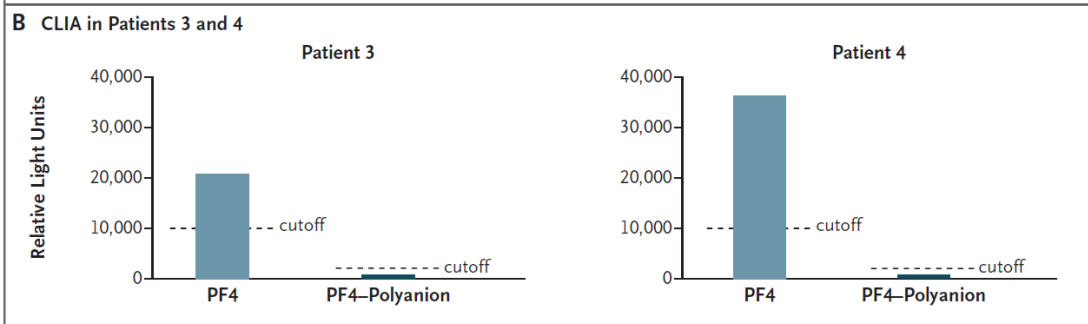
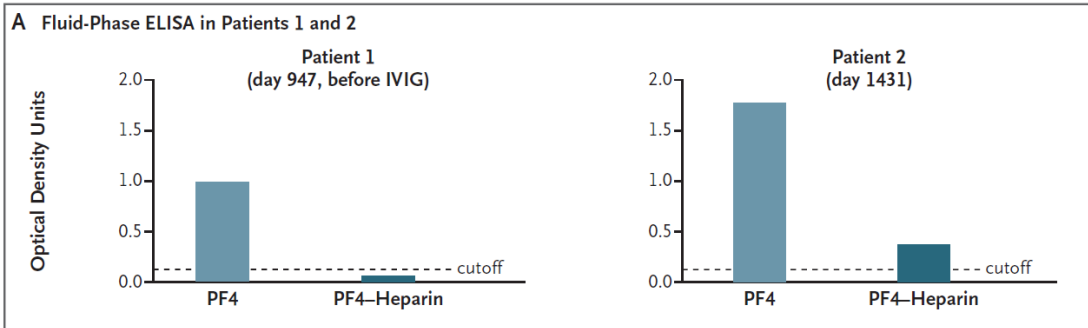


Table 1. Characteristics of Five Patients with VITT-like MGTS and Five Patients with Postviral VITT.*

Characteristic	VITT-like MGTS					Postviral VITT (N=5)
	Patient 1	Patient 2	Patient 3	Patient 4	Index Patient†	
Age at onset (yr)	60	46	35	47	79	Range, 5–58; one child
Sex	Male	Male	Male	Female	Female	Three female; two male
Duration of illness	4 yr	4 yr (died)	22 yr	5 yr	4 yr	Acute (weeks)
Initial platelet count (per mm ³)	152,000	199,000	44,000	50,000	250,000	Not reported
Platelet count nadir (per mm ³)	21,000	10,000 (at death)	23,000	30,000	81,000	Range, 10,000–38,000
Cerebral venous sinus thrombosis	No	Yes (fatal)	No	Yes	No	Yes in 3 patients
Splanchnic-vein, adrenal-vein, or renal-vein thrombosis	Yes (hepatic vein)	Yes (both adrenal veins)	Yes (mesenteric and splenic veins)	Yes (renal vein)	No	Yes in 1 patient
Deep-vein thrombosis	Yes	Yes	Yes	Yes	Yes	Yes in 2 patients
Superficial-vein thrombosis	No	Yes	No	Yes	No	Yes in 1 patient
Pulmonary embolism	Yes	No	Yes	Yes	Yes	Yes in 1 patient
Arterial thrombosis	Yes	No	Yes	No	Yes (arterial stroke)	Yes in 1 patient
Solid-phase PF4–polyanion ELISA‡	Positive (2.22 OD units)	Positive (2.29 OD units)	Positive (2.15 OD units)	Positive (2.30 OD units)	Positive (3.10 OD units)	Positive in all 5 patients
PF4–polyanion CLIA§	Negative	Negative	Negative	Negative	Negative	Negative in all 5 patients
Fluid-phase PF4 ELISA or PF4 CLIA¶	Positive fluid-phase ELISA (VITT-like)	Positive fluid-phase ELISA (VITT-like)	Positive CLIA (VITT-like)	Positive CLIA (VITT-like)	Positive CLIA (VITT-like)	Positive fluid-phase ELISA (VITT-like) in all 5 patients
Platelet-activation assay	Strongly positive SRA	Strongly positive SRA	Strongly positive PIPA	Strongly positive PIPA	Strongly positive PIPA	Strongly positive SRA in all 5 patients
M protein detected	Monoclonal IgGκ (0.29 g/dl)	Monoclonal IgGλ (<0.10 g/dl)	Monoclonal IgGλ (0.30 g/dl)	Monoclonal IgGλ (0.13 g/dl)	Monoclonal IgGκ (0.14 g/dl)	None
VITT-like anti-PF4 antibody identical to paraprotein	Yes	Yes	Yes	Yes	Yes	Not applicable



VITT-Like MGTS: Consideration

- ▶ **Testing for unexplained chronic prothrombotic disorders**
 - Anti-PF4 antibodies
 - M proteins (SPEP and immunoelectrophoresis)
- ▶ **Anti-PF4 monoclonal proteins are typically VITT-like**
 - Not HIT-like
 - Usually detectable on commercially available PF4-dependent ELISAs
- ▶ **May warrant therapeutic strategies beyond anticoagulation**
 - Recurrent thromboses despite anticoagulation
 - Catastrophic clinical course observed in some patients

Outline

- ▶ Monoclonal gammopathy with clinical significance (MGCS)
- ▶ Hematologic MGCS:
 - Cold agglutinin disease (CAD)
 - Cryoglobulinemia
 - Monoclonal gammopathy with thrombotic significance (MGTS)
- ▶ **Monoclonal gammopathy of renal significance (MGRS)**
- ▶ POEMS syndrome and neurologic MGCS
- ▶ TEMPI syndrome
- ▶ Cutaneous MGCS

Monoclonal Gammopathy of Renal Significance (MGRS)

- ▶ **A plasma cell or B-cell proliferation secretes a Mlg or Ig fragment resulting in kidney injury**
 - One or more kidney lesions related with “nephrotoxic” Mlg
- ▶ **Does not meet accepted criteria for malignancy**
 - No hematologic criteria for specific therapy
- ▶ **Epidemiology:**
 - About 1.5% of MGUS patients

Pathologic Classification of Diseases with Tissue Deposition or Precipitation of Monoclonal Ig

► Organized

Crystals	Fibrillar	Microtubular
Myeloma cast nephropathy	Light chain amyloidosis	Type I and type II cryoglobulinemic GN
Light chain proximal tubulopathy (with or without Fanconi syndrome)	Nonamyloid	Immunotactoid GN
Crystal-storing histocytosis	Fibrillary GN	GOMMID

► Non-organized (granular)

MIDD (Randall type)	Other
LCDD	Proliferative GN with monoclonal Ig deposits (PGNMID)
LHCDD	Waldenström macroglobulinemia
HCDD	

GOMMID, glomerulonephritis with organized microtubular monoclonal Ig deposits; MIDD, monoclonal immunoglobulin deposition disease; LCDD, light-chain deposition disease; LHCDD, light and heavy-chain deposition disease; HCDD, heavy-chain deposition disease

Pathologic Classification of Diseases with Tissue Deposition or Precipitation of Monoclonal Ig

► Organized

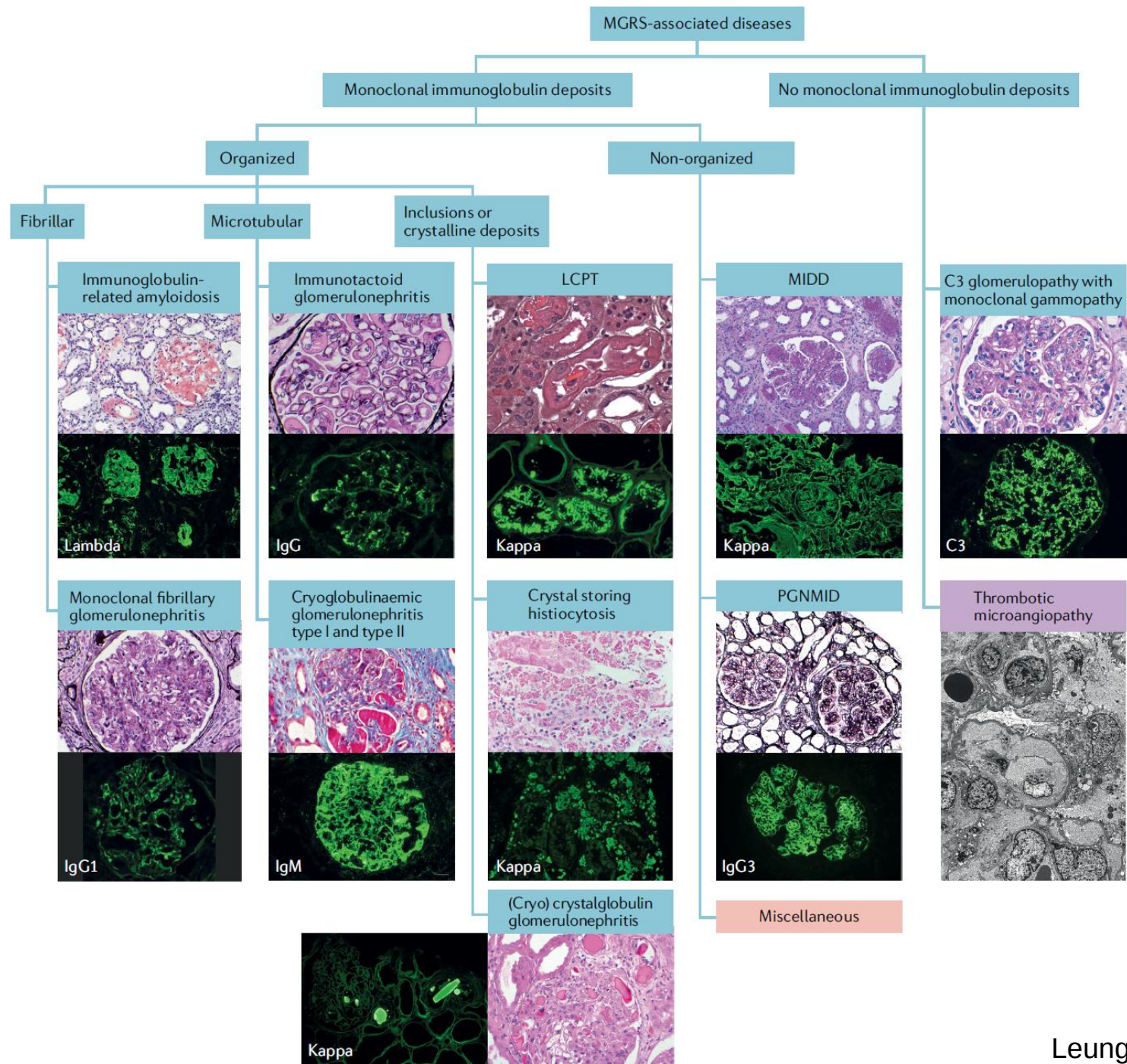
Crystals	Fibrillar	Microtubular
~~Myeloma cast nephropathy~~	Light chain amyloidosis	Type I and type II cryoglobulinemic GN
Light chain proximal tubulopathy (with or without Fanconi syndrome)	Nonamyloid	Immunotactoid GN
Crystal-storing histocytosis	Fibrillary GN	GOMMID

“MGRS”

► Non-organized (granular)

MIDD (Randall type)	Other
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GOMMID, glomerulonephritis with organized microtubular monoclonal Ig deposits; MIDD, monoclonal immunoglobulin deposition disease; LCDD, light-chain deposition disease; LHCDD, light and heavy-chain deposition disease; HCDD, heavy-chain deposition disease



Monoclonal Gammopathy of Renal Significance (MGRS)

Table 2. Monoclonal Gammopathy of Renal Significance Disorders: Main Characteristics

Disease	Renal Symptoms	Extrarenal Involvement	Identification of M-Protein
Glomerular disorders			
With organized Ig deposits			
AL amyloidosis	Proteinuria, nephrotic syndrome, and CKD; hypertension and hematuria uncommon	Frequent: heart, liver, peripheral nerve, and gastrointestinal tract	Serum EP/immunofixation: 66%-80% in AL, 85%-90% in AH/AHL; urine EP/immunofixation: 65%-70% in AL, 80% in AH/AHL; FLC: 75%-90% in AL, 80% in AH/AHL
AH amyloidosis			
AHL amyloidosis			
Immunotactoid glomerulonephritis/GOMMID	Proteinuria, nephrotic syndrome, CKD, microhematuria, hypertension	Uncommon: peripheral nerve and skin	Serum EP/immunofixation: 35%-70%; Urine EP/immunofixation: 20%-55%; FLC: 20%
Type I cryoglobulinemic glomerulonephritis	Proteinuria, nephrotic syndrome, CKD, microhematuria, and hypertension; possible nephritic syndrome, AKI, and anuria	Frequent: skin, peripheral nerve, and joints	Serum EP/immunofixation: 75%; Urine EP/immunofixation: UN; FLC: UN
With nonorganized Ig deposits			
MIDD	Proteinuria, nephrotic syndrome, CKD, microhematuria, and hypertension	Common, often asymptomatic: heart, liver, and lung	Serum EP/immunofixation: 25%-75% in LCDD, 80%-100% in LHCD, 67%-100% in HCDD; urine EP/immunofixation: 42%-90% in LCDD, 80%-100% in LHCD, 50%-100% in HCDD; FLC: 100% in LCDD, LHCD, HCDD
Proliferative glomerulonephritis with monoclonal immunoglobulin deposits	Proteinuria, nephrotic syndrome, CKD, microhematuria, and hypertension	None	Serum EP/immunofixation: 30%; urine EP/immunofixation: 10%; FLC: UN
C3 glomerulopathy with monoclonal gammopathy	Proteinuria, nephrotic syndrome, CKD, microhematuria, and hypertension	None	Serum EP/immunofixation: 100%; urine EP/immunofixation: 100%; FLC: 75%-100%
Tubular disorders			
Light chain Fanconi syndrome	Hypouricemia, hypophosphatemia, normoglycemic glycosuria, generalized aminoaciduria, low-molecular-weight proteinuria, proximal (type 2) renal tubular acidosis, and slowly progressive CKD	Bone: osteomalacia	
Proximal tubulopathy without crystals	Tubular proteinuria and progressive CKD	None	
Crystal-storing histiocytosis	Proximal tubule dysfunction and CKD	Bone marrow, liver, spleen, lymph nodes, lung, skin, and cornea	

Abbreviations: AH, immunoglobulin heavy chain; AHL, immunoglobulin heavy and light chain; AL, immunoglobulin light chain; AKI, acute kidney injury; CKD, chronic kidney disease; EP, electrophoresis; FLC, free light chain; GOMMID, glomerulonephritis with organized microtubular immunoglobulin deposits; HCDD, heavy chain deposition disease; Ig, immunoglobulin; LCDD, light chain deposition disease; LHCD, light and heavy chain deposition disease; MIDD, monoclonal immunoglobulin deposition disease; UN, unknown (adapted by Bridoux et al¹⁸).

Diagnosis of MGRS

- ▶ **Kidney biopsy: demonstration of monoclonal deposits in the kidney**
 - Immunofluorescence study
 - Restriction to single class of light chain and/or heavy chain
 - Equivocal results: further testing
 - Immunoelectron microscopy
 - Proteomics: laser dissection tandem mass spectrometry
- ▶ **Monoclonal protein studies: serum IFE, FLC**
- ▶ **Bone marrow study**

Leung N. Blood 2012;120:4292-5.
Ferland JP. Blood 2013;122:3583-90.
Castillo JJ. Am J Hematol 2021;96:846–53.
Leung N. Nat Rev Nephrol 2019;15:45-59.

Diagnosis of MGRS: Role of Kidney Biopsy

- ▶ **Recommended in the following patients:**
- ▶ Monoclonal gammopathy and unexplained kidney disease
- ▶ Known risk factors for CKD but an atypical clinical course
- ▶ Patients with kidney disease and monoclonal gammopathy aged <50 years

Must balance risks associated with

- Underdiagnosis of potentially treatable conditions
- Complications

Treatment of MGRS

- ▶ **The treatment should be tailored to the clone responsible**
- ▶ **Anti-plasma cell or anti B-cell therapy**
 - Novel agents e.g. bortezomib
 - ASCT in selected patients
- ▶ Recovery of renal function is possible with adequate hematologic response
- ▶ High risk of recurrence and dialysis

Outline

- ▶ Monoclonal gammopathy with clinical significance (MGCS)
- ▶ Hematologic MGCS:
 - Cold agglutinin disease (CAD)
 - Cryoglobulinemia
 - Monoclonal gammopathy with thrombotic significance (MGTS)
- ▶ Monoclonal gammopathy of renal significance (MGRS)
- ▶ **POEMS syndrome and neurologic MGCS**
- ▶ TEMPI syndrome
- ▶ Cutaneous MGCS

POEMS Syndrome

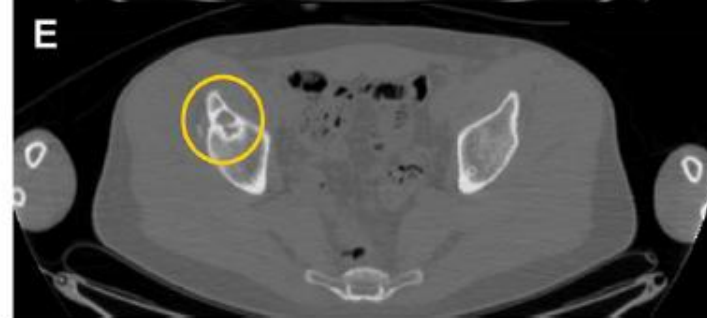
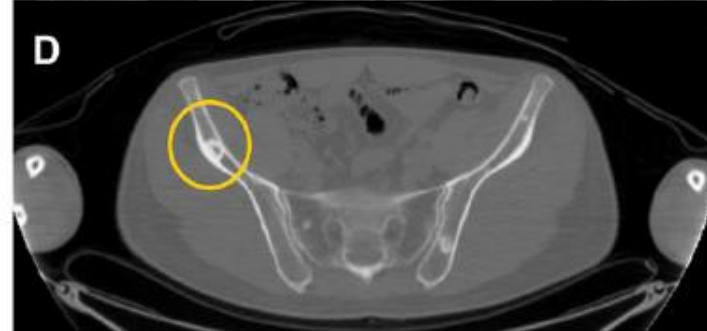
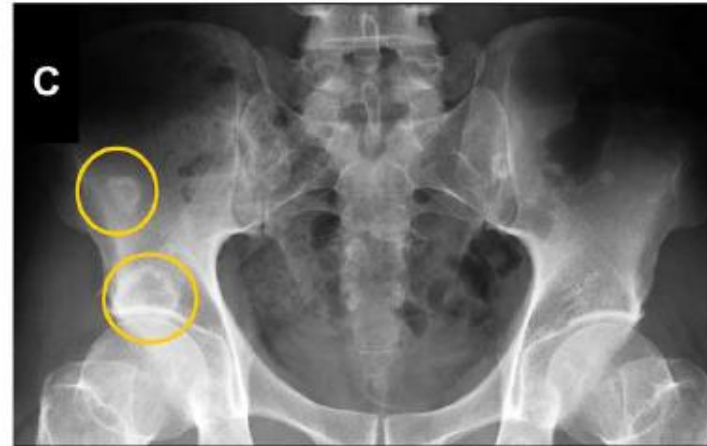
- ▶ **Paraneoplastic syndrome due to an underlying plasma cell neoplasm**
 - **P**olyneuropathy
 - **O**rganomegaly
 - **E**ndocrinopathy
 - **M**onoclonal plasma cell disorder (M protein)
 - **S**kin changes
- ▶ **Other important features: PEST**
 - **P**apilledema, **E**xtravascular volume overload, **S**clerotic bone lesions, **T**hrombocytosis/erythrocytosis

POEMS Syndrome: Diagnosis

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 hemangiomas, 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

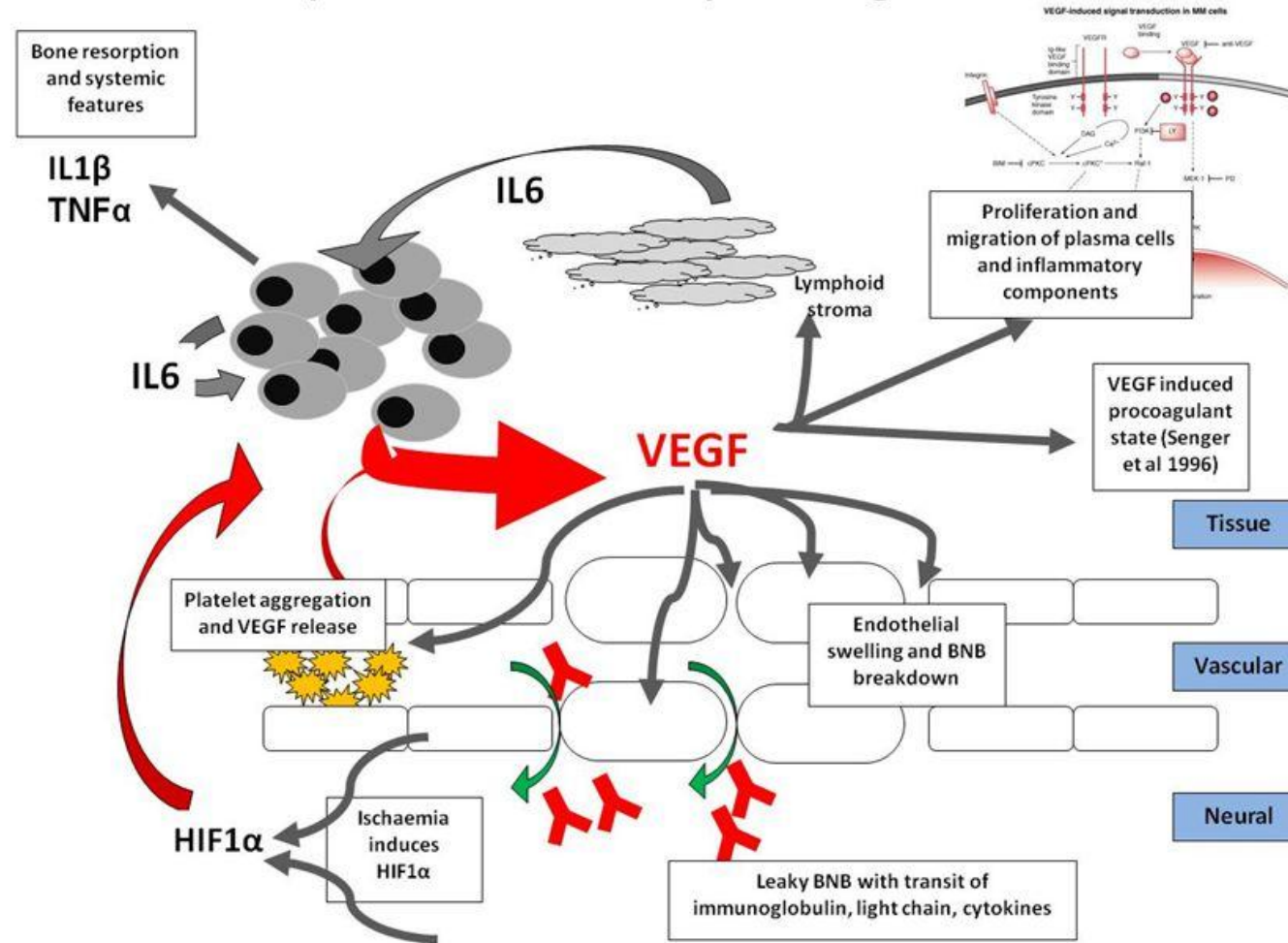
- ▶ **Both mandatory criteria +**
- ▶ **One major criteria +**
- ▶ **One minor criteria**

POEMS Syndrome



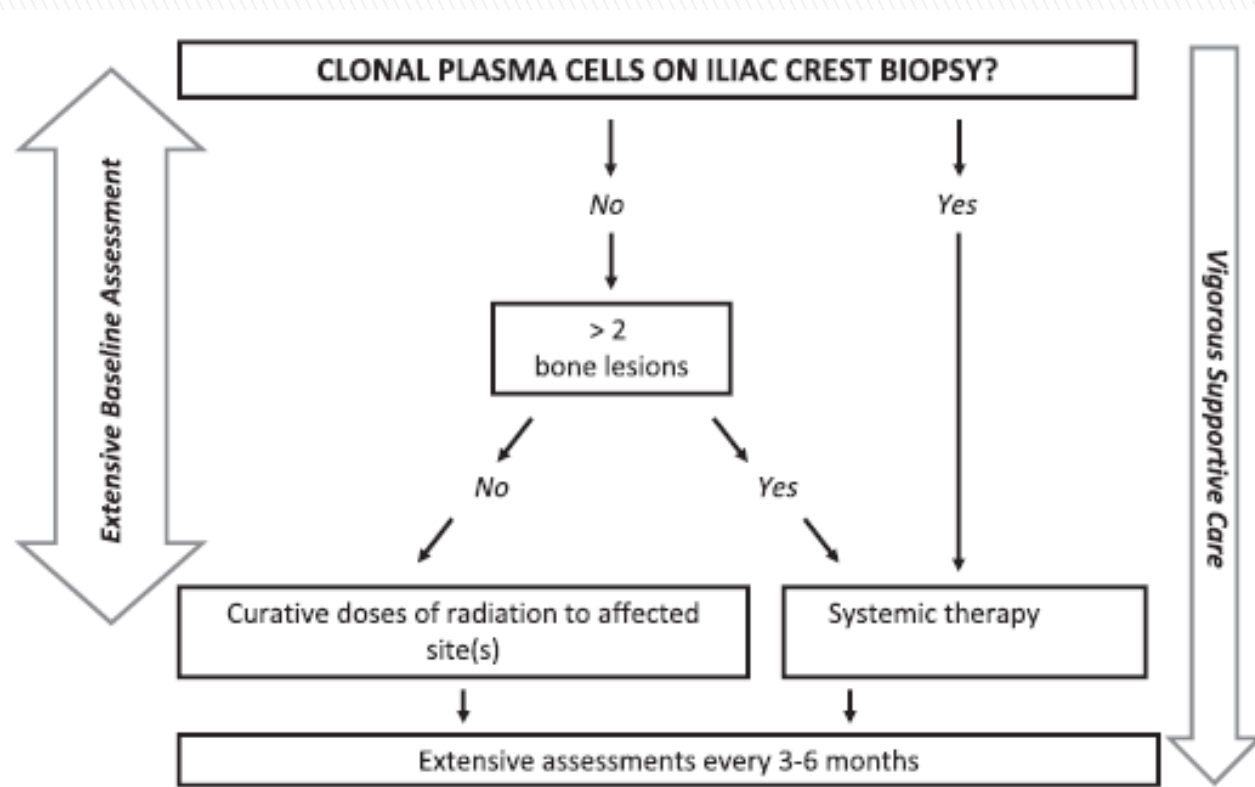
POEMS Syndrome: Pathogenesis

Proposed POEMS pathogenesis



POEMS Syndrome: Treatment

Algorithm of treatment



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

Case Presentation

► Management:

◦ **Plasmacytoma with POEMS**

- Denied RT
- Melphalan-Dexamethasone 12 cycles → stringent CR
- Relapsed at 3 years: Cyclophosphamide-Dexamethasone
- Neurological symptoms: improved, can walk and do ADL

◦ **STEMI**

- Medical treatment → no recurrent symptoms

Monoclonal Gammopathy of Neurological Significance (MGNS)

- ▶ **MGUS and peripheral neuropathy (PN)**
- ▶ IgM > IgG, IgA paraproteins
- ▶ MGNS usually refers to IgM-mediated PN
- ▶ **IgG and IgA PN**
 - Heterogenous clinical and electrophysiological features
 - No specific antibody
 - Can be indistinguishable from CIDP
 - Treatment as CIDP

Monoclonal Gammopathy of Neurological Significance (MGNS)

- ▶ **MGUS and peripheral neuropathy (PN)**
- ▶ IgM > IgG, IgA paraproteins
- ▶ MGNS usually refers to IgM-mediated PN
- ▶ **IgM-mediated PN (IgM MGUS PN)**
 - Typical sensory PN, symmetrical, length-dependent
 - Slow progression
 - “Distal acquired demyelinating symmetric neuropathy with monoclonal gammopathy (DADS-M)”

Monoclonal Gammopathy of Neurological Significance (MGNS)

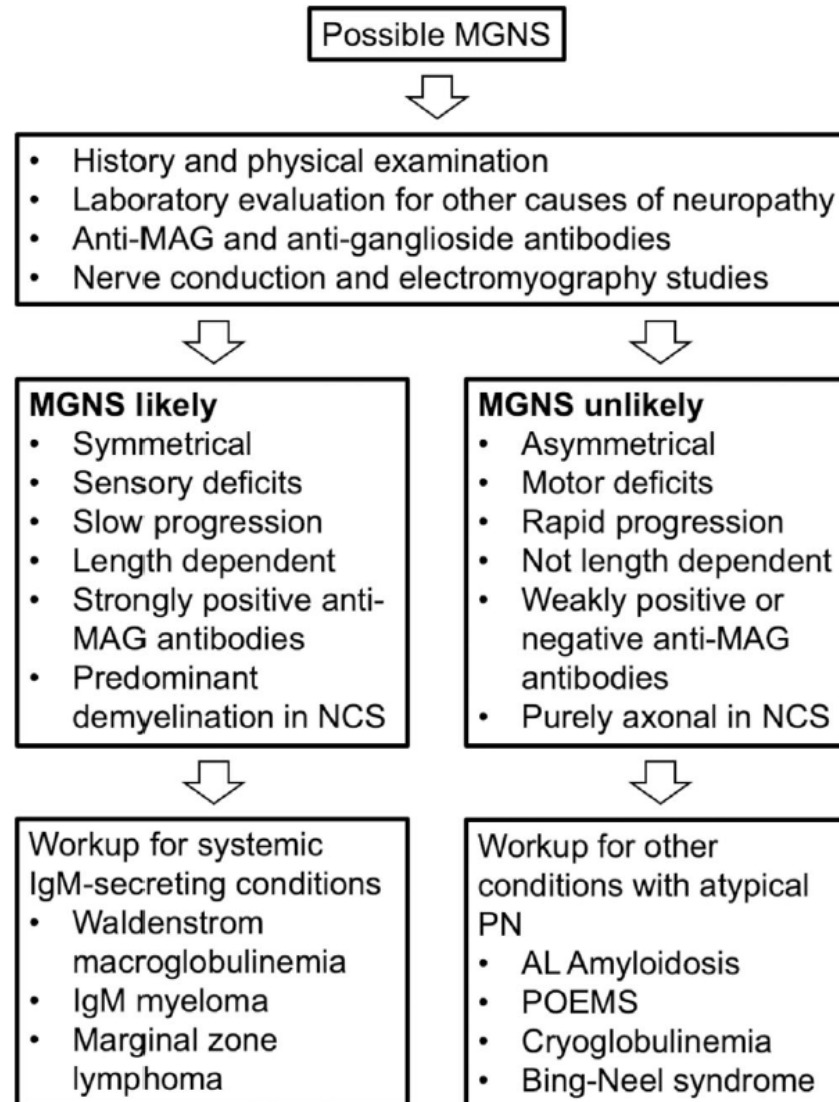
▶ DADS-M

- 50% disability 10-15 years after diagnosis
- 50% had anti-MAG antibody (high titer = clinically significant)
 - Others: antibodies against gangliosides and sulphate-3-glucuronyl paragloboside (SGPG)

▶ CANOMAD

- Chronic ataxic neuropathy with ophthalmoplegia, monoclonal gammopathy, cold agglutinins, and disialosyl ganglioside antibodies (anti-GD1b, anti-GT1b or anti-GQ1b)
- Rare condition
- NCS show mixed axonal and demyelinating features

Proposed Algorithm for Evaluation of MGNS



Treatment of MGNS

- ▶ **Limited data**
- ▶ **Treatment in case with PN affecting ADL**
- ▶ **Immunomodulating therapy**
 - IVIG, steroids, plasma exchange
 - Low response rate
- ▶ **Waldenstrom macroglobulinemia (WM)-based treatment**
 - Rituximab
 - Avoid neurotoxic agents such as bortezomib and vincristine

Outline

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- ▶ POEMS syndrome and neurologic MGCS
- ▶ **TEMPI syndrome**
- ▶ Cutaneous MGCS

TEMPI Syndrome

- ▶ **Rare and acquired disorder characterized by 5 salient features, which compose its name:**
- ▶ **(1) telangiectasias**
- ▶ **(2) elevated erythropoietin and erythrocytosis**
- ▶ **(3) monoclonal gammopathy**
- ▶ **(4) perinephric fluid collections**
- ▶ **(5) intrapulmonary shunting**

TEMPI Syndrome

► Diagnostic criteria

Major
Telangiectasias
Elevated erythropoietin and erythrocytosis
Monoclonal gammopathy
Minor
Perinephric fluid
Intrapulmonary shunting
Other
Venous thrombosis

A diagnosis is primarily made on clinical and imaging investigations

TEMPI Syndrome

- ▶ **Pathophysiology**
- ▶ Plasma cell–secreted circulating factor ?



Oxygen-sensing machinery: HIF1 α (?)

- ▶ Unregulated production of erythropoietin



- ▶ Development of telangiectasias, pulmonary shunting, and perinephric fluid collections

TEMPI Syndrome

Clinical manifestations

Table 1. Characteristics of Patients with the TEMPI Syndrome.*

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Demographic						
Age (yr)	42	36	39	35	56	36
Sex	Male	Female	Female	Male	Male	Male
Year of presentation	2001	2005	1991	1978	1970	2002
Geographic location	Memphis, TN	Antwerp, Belgium	Los Angeles	Manchester, U.K.	Seattle	Indianapolis
Race or ethnic group	White	Belgian	Indian	White	Finnish	Mexican
TEMPI syndrome						
Telangiectasias, most prominent over the face, trunk, arms, and hands	Yes	Yes	Yes	NR	Yes	NR
Erythrocytosis	Yes	Yes	Yes	Yes	Yes	Yes
Hematocrit at presentation (%)	58	64	58	62	66	73
Erythropoietin (mU/ml)						
First measurement	16	50	600	NR	Increased	38
Highest value	>5000	>5000	>5000	>500	Increased	NR
Monoclonal gammopathy	IgG kappa	IgG kappa	IgG kappa	NR	IgG	NR
MGUS	Yes	Yes	Yes	NR	NR	NR
Perinephric fluid between the kidney and the renal capsule, without parenchymal renal cysts	Yes	Yes	Yes	Yes	NR	Yes
Requiring surgical marsupialization	Yes	No	Yes	Yes	No	Yes
Intrapulmonary shunting, microscopic	Yes	Yes	Yes	NR	Yes	NR
Hypoxemia	Yes	Yes	Yes	NR	Yes	Yes
Other						
Venous thrombosis†	Yes	Yes	Yes	NR	NR	NR
Spontaneous intracranial hemorrhage	No	Yes	Yes	NR	NR	NR

* Race or ethnic group was reported by the investigators. MGUS denotes monoclonal gammopathy of unknown clinical significance, and NR not reported.

† Thrombosis involved the internal jugular vein in Patient 1, the cerebral venous sinus in Patients 2 and 3, and the common femoral vein in Patient 3.

TEMPI Syndrome: Telangiectasias



TEMPI Syndrome

- ▶ **Treatment**
- ▶ **Plasma cell-directed therapy: rapid and remarkable response**
 - Bortezomib
 - Lenalidomide
 - ASCT from melphalan-based conditioning regimen
 - Daratumumab ?
- ▶ Serum erythropoietin as sensitive marker for relapsed

Outline

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- ▶ **Cutaneous MGCS**

Cutaneous MGCS

Table 1. Monoclonal gammopathies and associated skin diseases.

Group I

- Waldenström macroglobulinemia
- Systemic immunoglobulin light chain amyloidosis
- Cryoglobulinemia
- Plasmacytoma
- Osteosclerotic myeloma (POEMS syndrome)

Group II

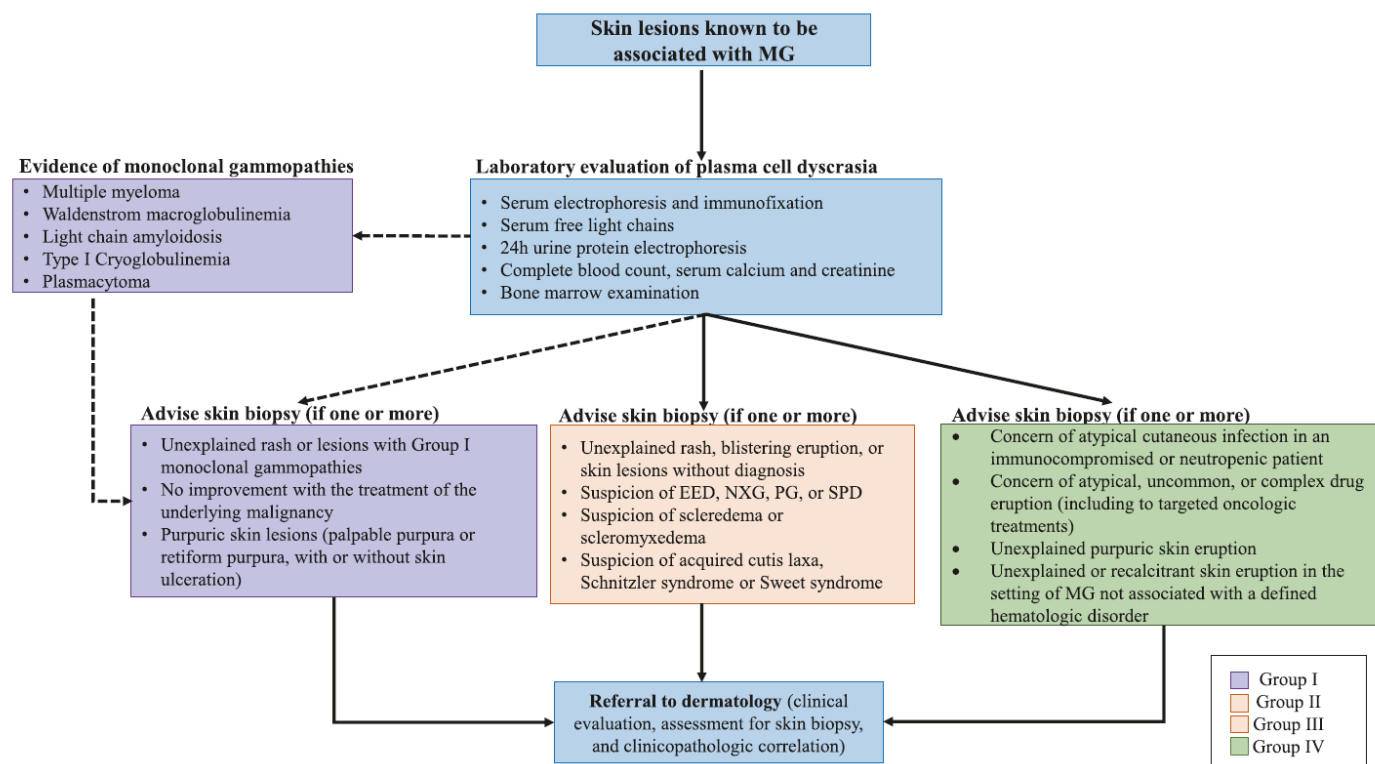
- High association
 - Scleromyxedema
 - Scleredema
 - Necrobiotic xanthogranuloma
 - Plane xanthoma
 - Schnitzler syndrome
- Low association
 - Pyoderma gangrenosum
 - Sweet syndrome
 - Leukocytoclastic vasculitis
 - Neutrophilic dermatosis
- Unknown
 - Erythema elevatum diutinum
 - Subcorneal pustular dermatosis

Group III

- Miscellaneous cutaneous disorders described in association with monoclonal gammopathies

Group IV

- Miscellaneous cutaneous signs or symptoms including purpura, pruritis, infection, adverse reactions to medications, etc.



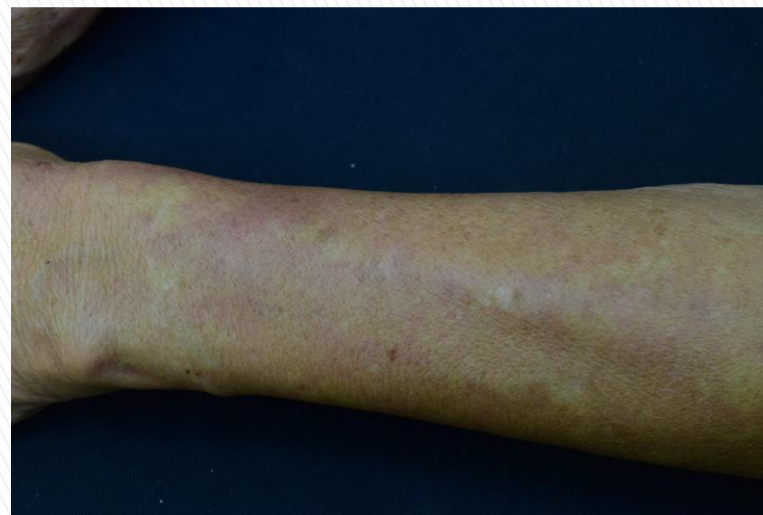
Management algorithm of cutaneous manifestations associated with MG

EED erythema elevatum diutinum, NXG necrobiotic xanthogranuloma, PG pyoderma gangrenosum, SPD subcorneal pustular dermatosis

Cutaneous MGCS: Schnitzler Syndrome

Schnitzler syndrome classification diagnostic criteria

Mandatory major criteria	• Chronic urticarial rash • Presence of monoclonal IgM or IgG gammopathy
Minor criteria	• Recurrent fever • Abnormal bone remodeling with or without pain • Neutrophilic dermatosis on skin biopsy • Leukocytosis and/or elevated C-reactive protein (CRP)
Definite diagnostic	• Two mandatory major criteria and at least 2 minor criteria if IgM and at least 3 minor criteria if IgG
Probable diagnostic	• Two mandatory major criteria and at least 1 minor criteria if IgM and at least 2 minor criteria if IgG



Picture
courtesy of
Dr.Chonlada
Laoruangroj

Cutaneous MGCS



Scleromyxedema

Firm, waxy, dome-shaped papules of the dorsal fingers and hand

Discrete and coalescing, firm papules of the posterior ear and postauricular region



Scleredema

Lower extremity ulcerations associated with woody induration and erythema

Conclusions

- ▶ **Many faces of monoclonal gammopathy-related disorders**
- ▶ **Hematologic MGCS**
 - CAD: IgM MGUS → cold AIHA
 - Cryoglobulinemia (type 1)
 - MGTS: VITT-like antibody
- ▶ **MGRS: MGUS → nephrotoxic / nephrotic-nephritis**
- ▶ **POEMS: VEGF → neurotoxic / polyneuropathy**
- ▶ **TEMPI syndrome: MGUS → increase erythropoietin**
- ▶ **Cutaneous MGCS**
 - Schnitzler syndrome: urticaria

Thank You for Your Attention