



**CBCI**

COLORADO BLOOD  
CANCER INSTITUTE  
AT PRESBYTERIAN/ST. LUKE'S

# **The Basics of Waldenström's Macroglobulinemia (WM)**

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# Objectives

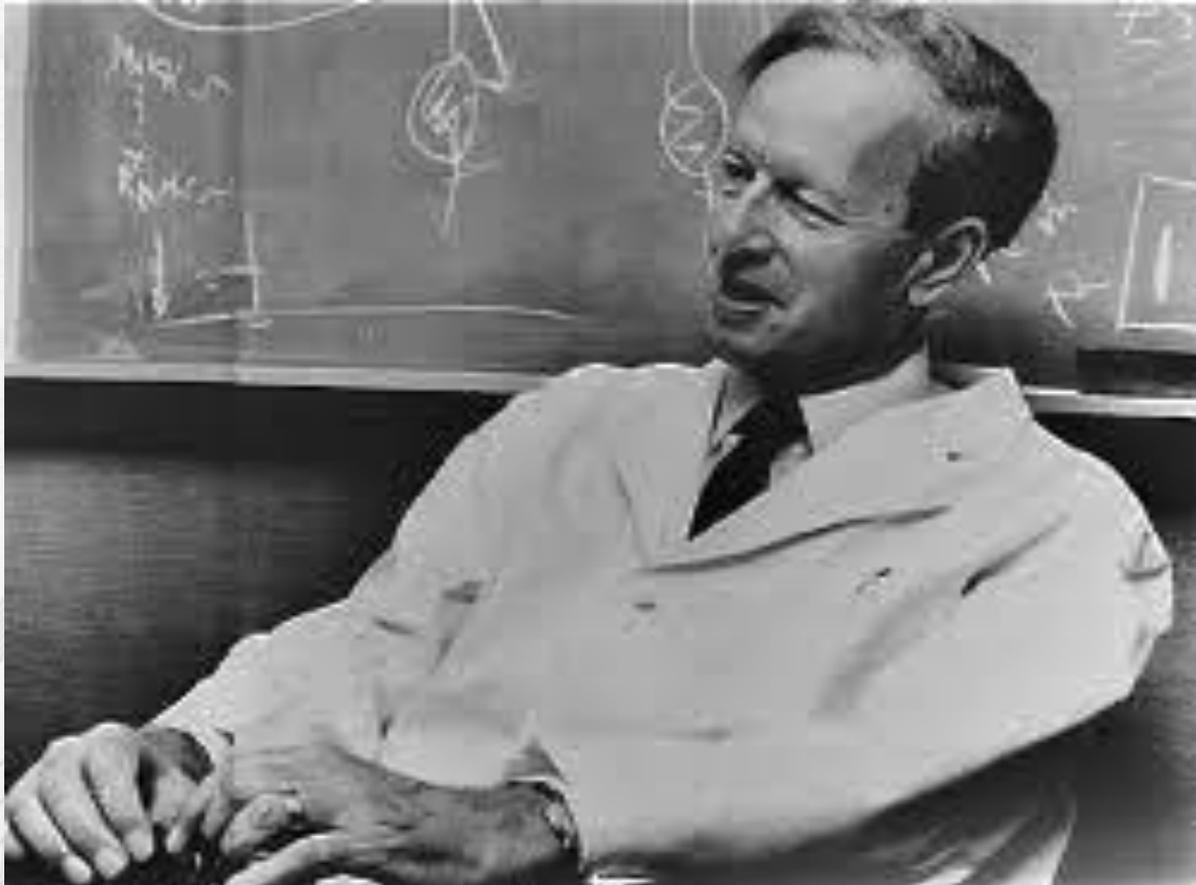
- ◆ Describe pathobiology of malignant cellular development
- ◆ Review incidence, possible risk factors and clinical presentation
- ◆ Explain diagnosis, symptoms, and treatment guidelines

# What is Waldenström's Macroglobulinemia?

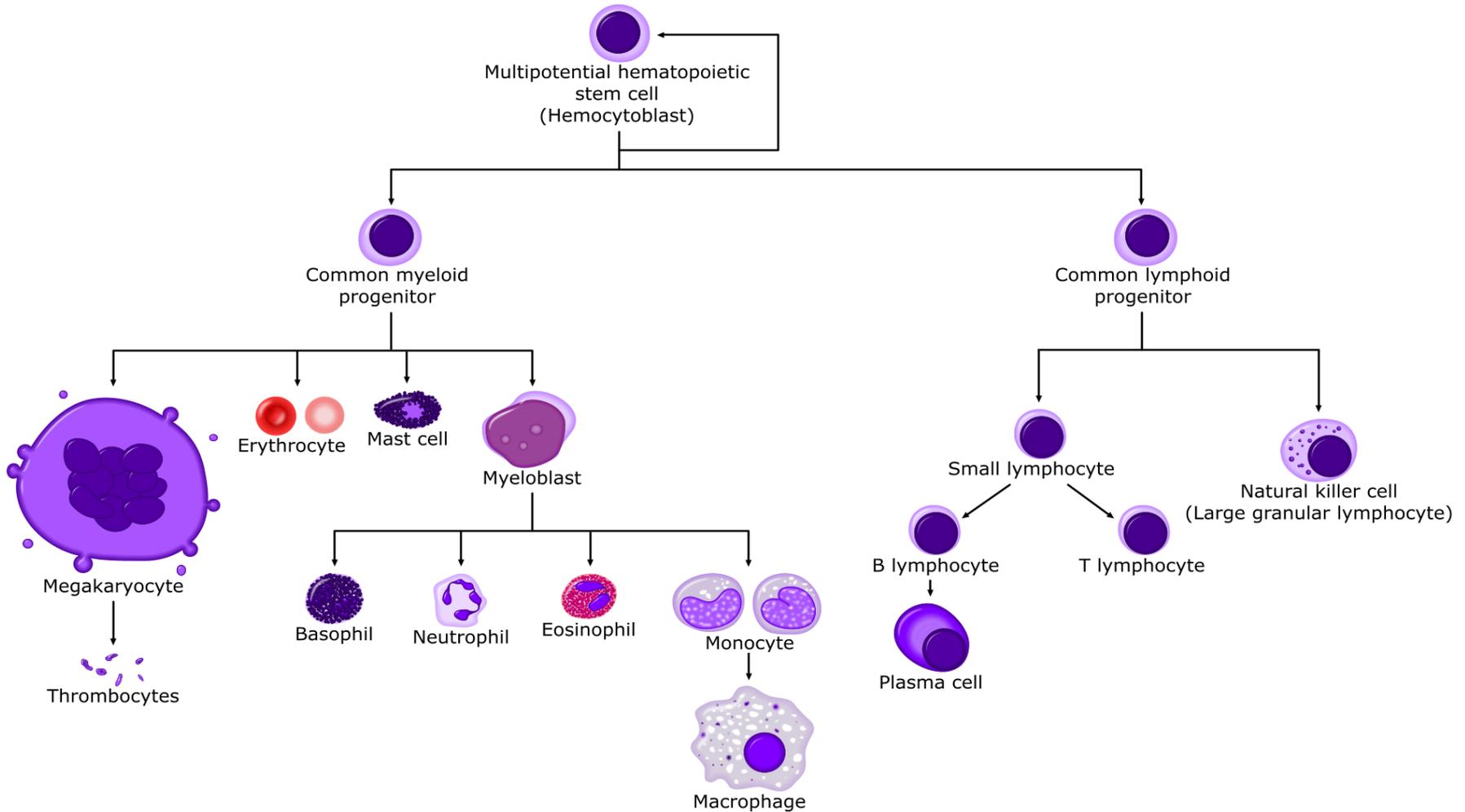
- ◆ WM is a blood cancer
  - Occurs when lymphocytes and plasma cells reproduce out of control
  - These cells don't undergo normal programmed cell death
  - WM cells make excess antibodies (always IgM), which are heavy proteins
  - Named after Jan Waldenström – Swedish oncologist (first identified in 1944)



# Dr. Waldenström



# How are blood cells produced?



# What is Waldenström's Macroglobulinemia? (cont)

- ◆ Rare cancer affecting 3 in 1 million/year
- ◆ 1500 new diagnosis in the U.S. each year
- ◆ Median age at diagnosis is 64
- ◆ 60% of patients are male
- ◆ More common in Caucasians than other ethnic groups
- ◆ Familial disposition present ~20% cases

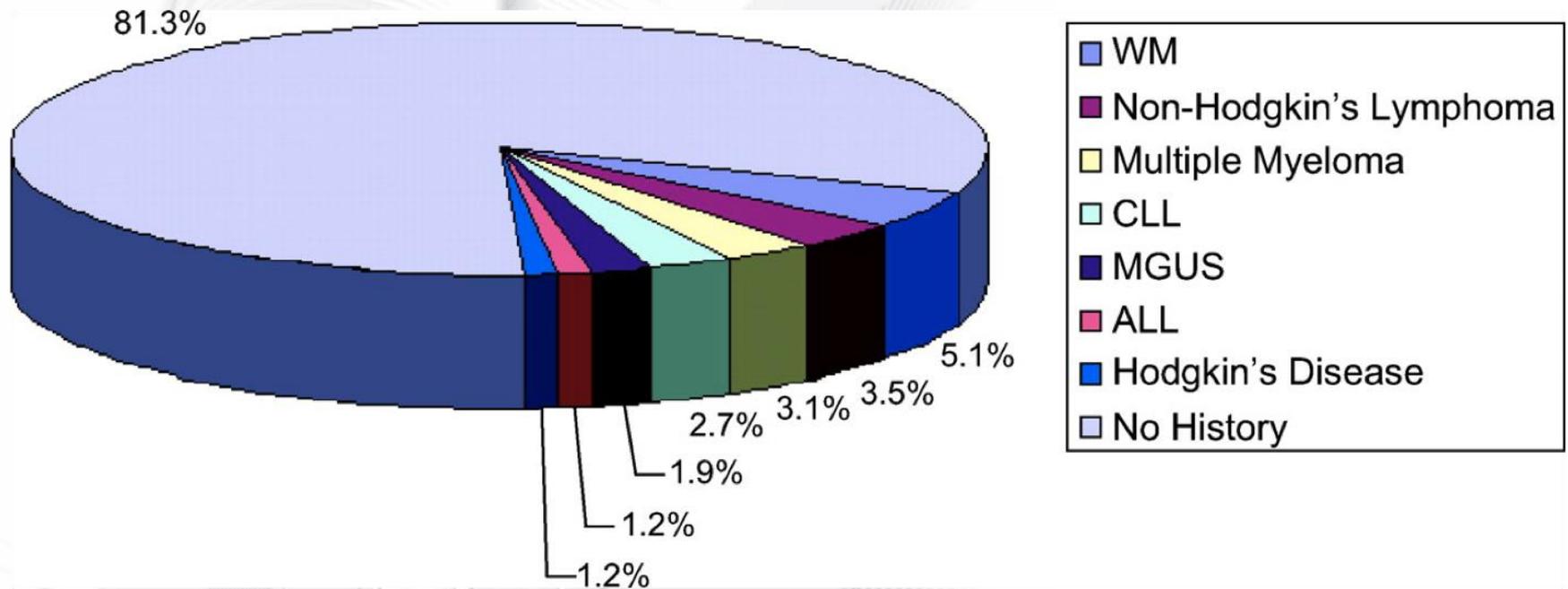
# REAL/WHO definition

- ◆ Lymphoplasmacytic lymphoma (LPL)
  - IgM secretion
  - LPL cells in the bone marrow
- ◆ Symptomatic vs. asymptomatic (smoldering)
  - Symptomatic needs to be treated
  - Asymptomatic does not need to be treated
- ◆ MGUS with IgM protein

# What causes WM?

- ◆ Most cases are sporadic
- ◆ About 20% are familial with at least 1 first degree relative with WM or another B cell disorder
- ◆ Main risk factor is the presence of MGUS (10% yearly progression)

# Reported hx of B-cell disorders among 1<sup>st</sup> degree relatives of 257 pt with WM



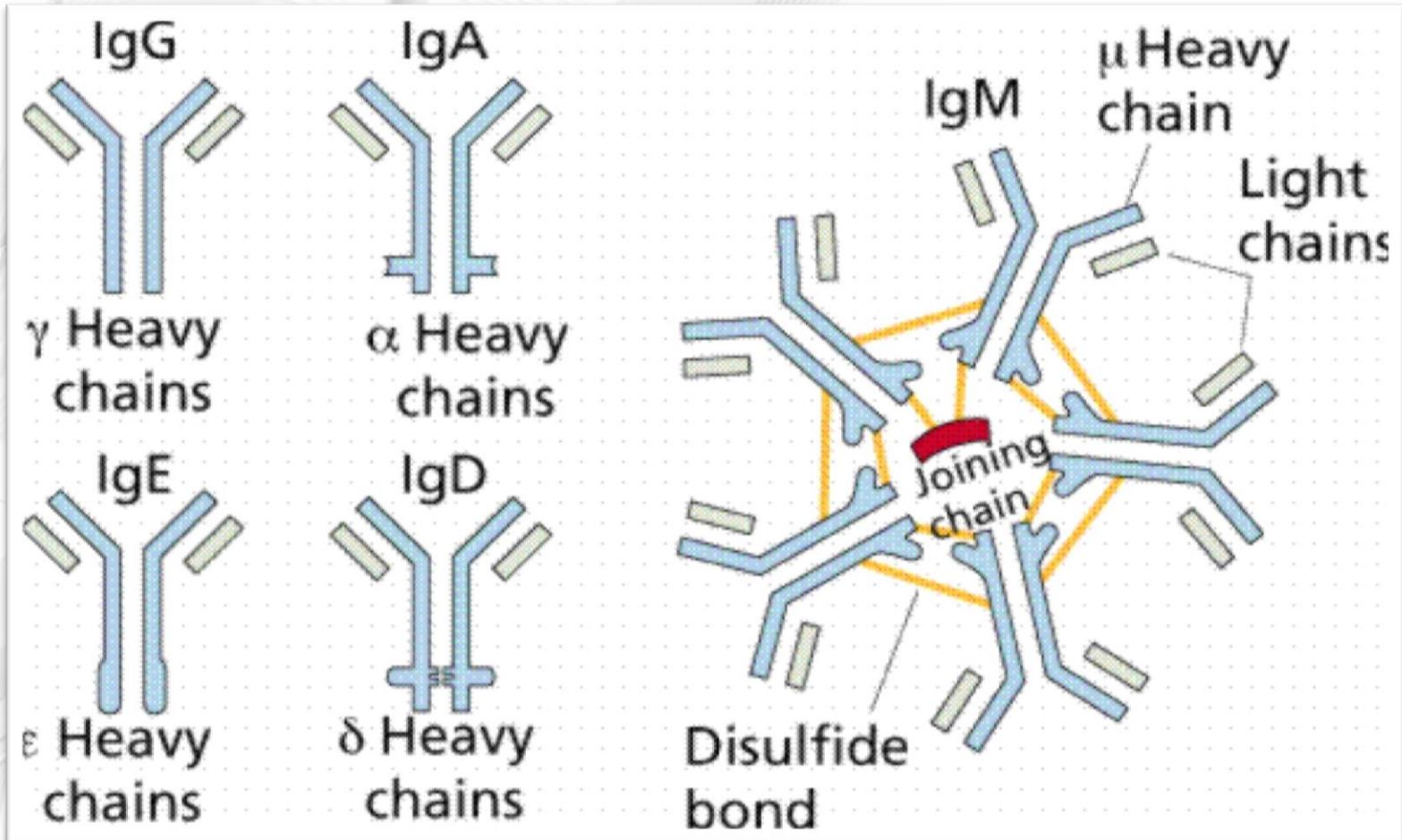
Teon S P et al. Ann Oncol 2006;17:488-494

# Qigs

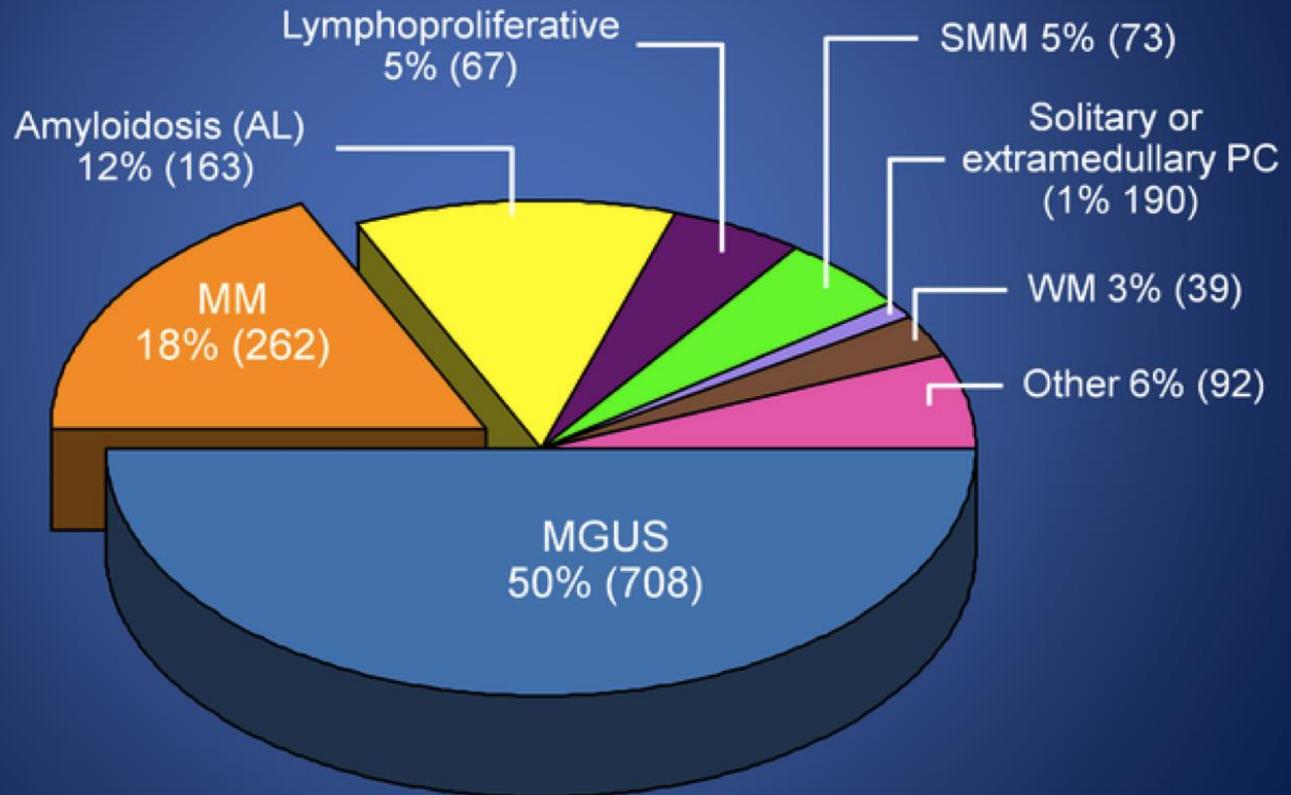
## (Quantitative Immunoglobulins)

- ◆ Measures the absolute number of IgM, IgG and IgA proteins
- ◆ In WM patients, IgM is HIGH and the other numbers are usually LOW
  - IgG (700-1600 MG/DL)
  - IgA (70-400 MG/DL)
  - IgM (40-230 MG/DL)
- ◆ Low numbers of IgA and IgG can lead to an increased risk of infection

# Qigs (Quantitative Immunoglobulins)



# Distribution of Monoclonal Gammopathies Mayo Clinic Experience (N = 1423)



Rajkumar SV, Kyle RA. Plasma cell disorders. In: Goldman L, Ausiello D, eds. *Cecil Medicine*. 23rd ed. Philadelphia, PA: Saunders; 2008:1426-1437.

# Typical BM Biopsy Report in a patient with WM

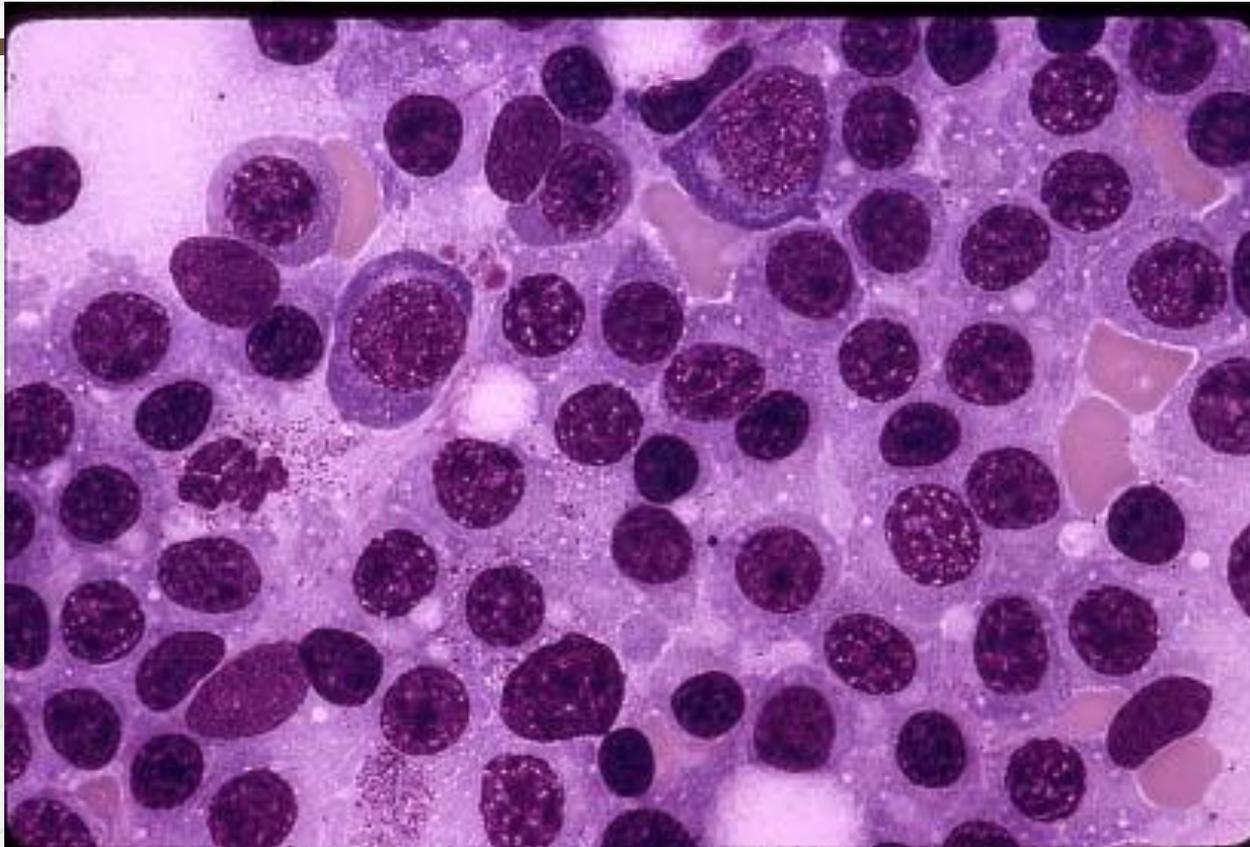
## BONE MARROW BIOPSY:

Variably cellular, overall mildly to moderately hypocellular marrow (60-70% fat).

Approximately 30-40% of the cellularity and 10-20% of intertrabecular space is comprised of a predominantly nodular and interstitial population of small to intermediate sized lymphocytes, plasma cells, and lymphoplasmacytoid forms.

**Mast cells are seen in association with the lymphoid aggregates.**

# Lymphoplasmacytic cells



Aspirate from a patient with WM demonstrating excess mature lymphocytes, lymphoplasmacytic cells and plasma cells (courtesy of Marvin Stone M.D.)

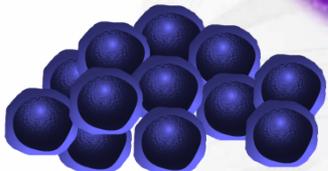
# Presenting Symptoms of WM

◆ Weakness and fatigue	44%
◆ Hemorrhagic manifestations	44%
◆ Weight loss	23%
◆ Neurologic symptoms	11%
◆ Visual disturbances	8%
◆ Reynaud's phenomenon	3%

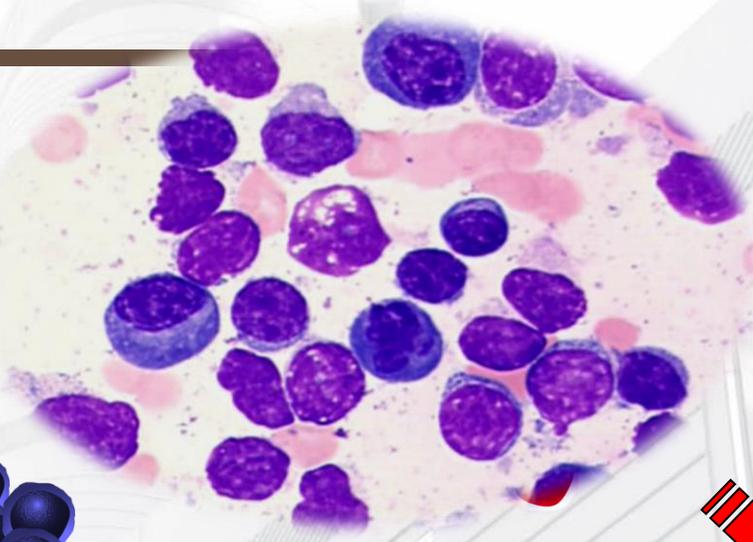
# WM Clinical Features

◆ Tumor infiltration	
– Bone marrow	90%
– Splenomegaly	38%
– Lymphadenopathy	30%
◆ Circulating IgM	
– Hyperviscosity syndrome	15-20%
– Cryoglobulinemia	5-15%
– Cold agglutinin disease	5-10%
– Bleeding disorders	10%
◆ Tissue IgM	
– Neuropathy	10-20%

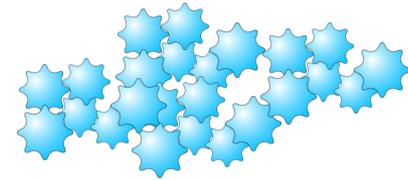
**↓HCT, ↓PLT, ↓WBC**



Adenopathy,  
splenomegaly  
≤20%



Fatigue, Sweats  
Cytokinememia?



Hyperviscosity  
Syndrome:  
Epistaxis, HA,  
Impaired vision  
>4.0 CP



IgM Neuropathy (22%)  
Cryoglobulinemia (10%)  
Cold Agglutininemia (5%)

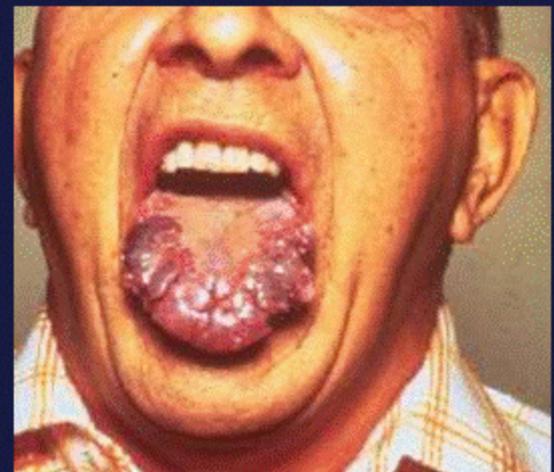


# How does WM make too much protein?

- ◆ Clonal lymphocytes and plasma cells (WM cells)
  - Secrete IgM
    - Immunoglobulin (protein) used to fight infection
  - Increased IgM may lead to increased total protein in the blood
  - Can measure levels of IgM with quantitative immunoglobulin blood test (Qig' s)
  - Can measure levels of clonal IgM with SPEP+M

# Hyperviscosity Syndrome and Amyloidosis

- Typically associated with serum viscosity >4 units (normal range, 1.4–1.8 units)
- Increased concentration of M protein can coat RBCs and make them “sticky”
  - Hemolysis and sludging cause circulatory occlusion
  - Impaired circulation in retinal vessels
  - Can cause clotting abnormalities
- Confusion and mental status changes
- Amyloidosis results from deposit of M protein within tissues of body
  - May result in heart/kidney failure or disruption of nerves



# Serum Viscosity

- ◆ Measures the resistance of fluid to flow
  - Water flows readily, less viscous = “thin”
  - Oil flows less readily, more viscous = “thick”
- ◆ IgM proteins make the blood more viscous
  - Can be mild and not cause symptoms
  - Or can thicken the blood causing headaches, nosebleeds, vision changes, or serious medical problems
  - May need plasma exchange to remove IgM and then treat underlying production

# Therapeutics in Waldenstrom's macroglobulinemia

*The use of plasmapheresis should be reserved for the treatment of symptomatic hyperviscosity, and for the treatment of certain complications of WM such as moderate to severe IgM related neuropathies or light chain related nephropathies. In such circumstances, plasmapheresis should be regarded as interim therapy until definitive therapy can be initiated and shown to control disease.*

**Semin Oncol 30:121, 2003**

# Prognosis

## Pay very little attention to what you read

### Prognosis in WM

- ISSWM
- 587 patients at first therapy

Risk	Low	Intermediate	High	
Age > 65 years	-	X	} > 2 factors	
Hb ≤ 11.5 g/dL	} ≤ 1 factor	or		
Platelet ≤ 100 x10 <sup>9</sup> /L		} 2 factors		
B2M > 3 mg/L				
IgM > 7 g/dL				
N (%)	158 (27%)	223 (38%)	206 (35%)	
Survival at 5 years	87%	68%	36%	P<0.001

Hb : hemoglobin; B2M : beta2-microglobulin; N : number of patients; % : percentage

*Morel et al, Blood 2009*

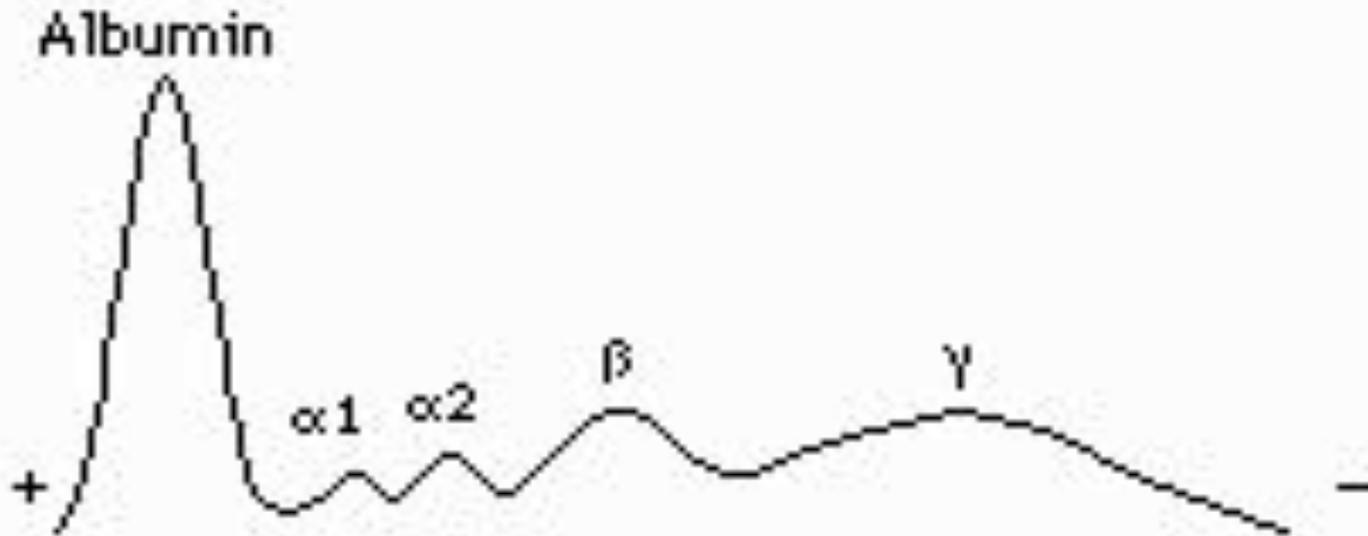
# What tests do we perform in a patient suspected of having WM?

- ◆ Blood work
- ◆ Urine test (looking for amyloid or other rare kidney issues)
- ◆ Bone marrow biopsy
- ◆ Sometimes CT scans
  
- ◆ Most important: talk to the patient!

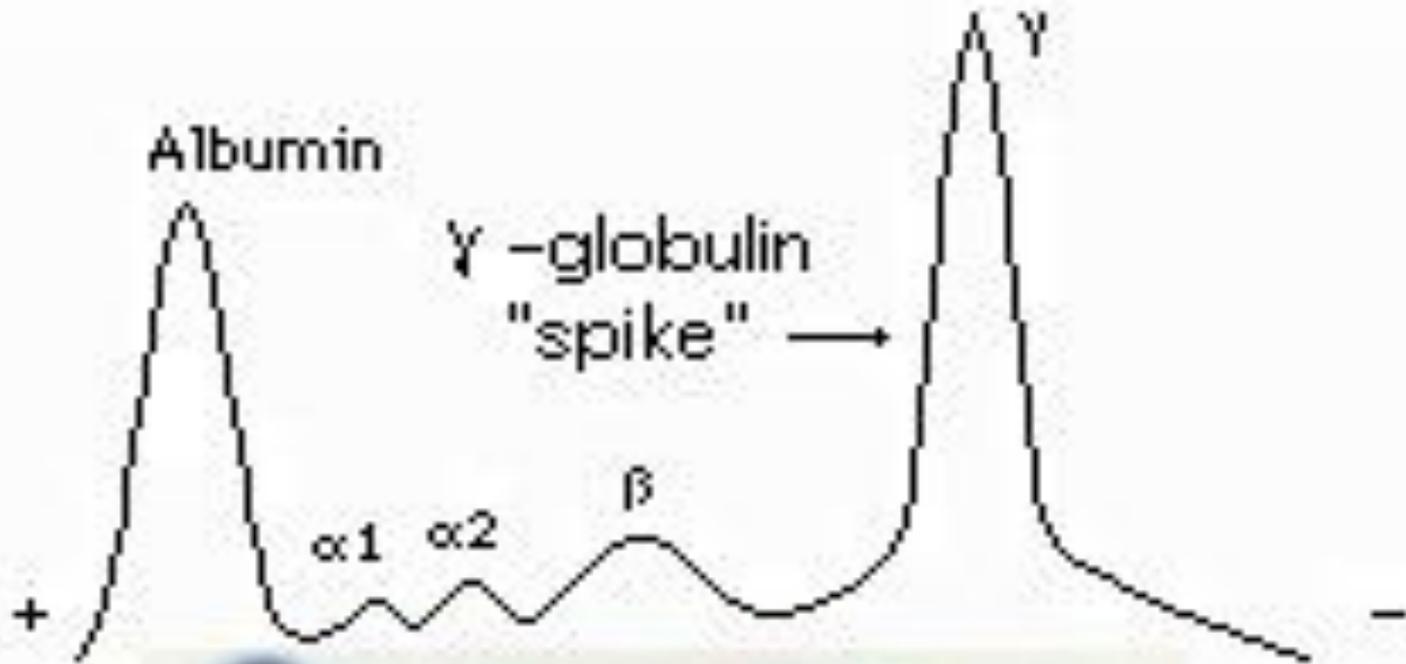
# Lab Evaluation

- ◆ Qig' s
- ◆ Serum Viscosity
- ◆ SPEP + M protein
- ◆ FLC assay
- ◆ Chemistry (total protein, calcium, renal function)
- ◆ CBC (cytopenias)
- ◆ MYD88 and perhaps CXCR4

# SPEP + M-protein (normal) (serum protein electrophoresis + M)

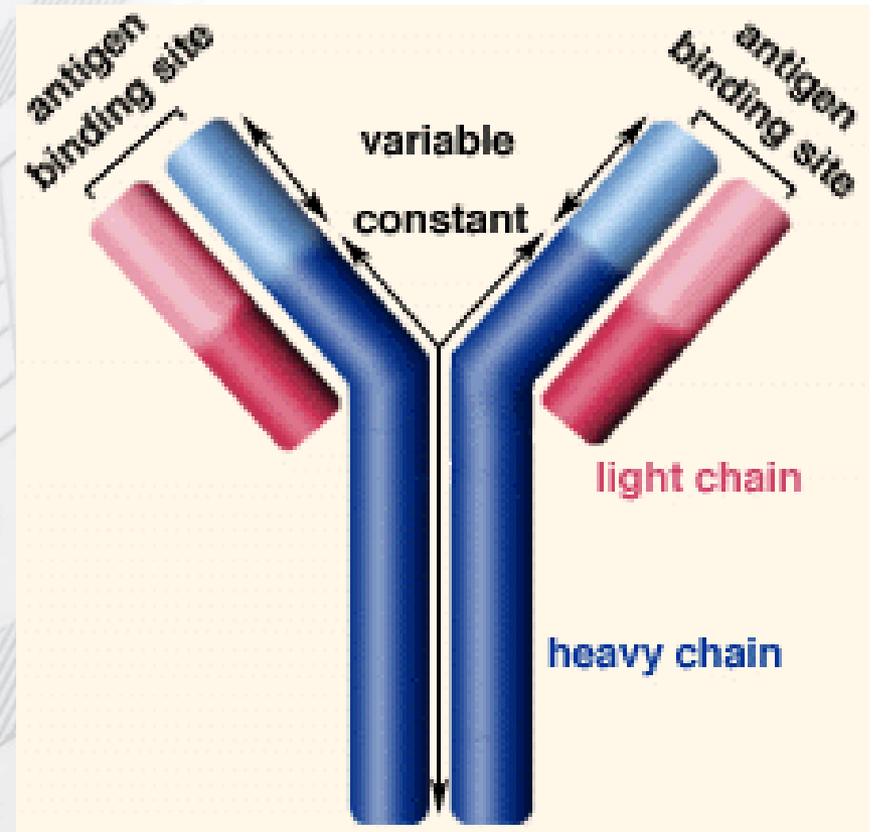


# SPEP + M-protein (abnormal) (serum protein electrophoresis + M)



# Free Light Chain Assay

- ◆ Measures kappa and lambda light chains not attached to the heavy chain (hence the term “free”)
- ◆ Lambda (3.3-19.4 mg/L)
- ◆ Kappa (5.71-26.3 mg/L)
- ◆ Ratio (0.26-1.65)



# Serum Chemistry

- ◆ Total protein
- ◆ Assess for hypercalcemia
- ◆ Assess for renal disease



# Complete Blood Count (CBC)

- ◆ WM patients are at risk for cytopenias
  - Leukopenia
  - Anemia
    - From underproduction of red cells secondary to a packed marrow
    - Hemolysis
  - Thrombocytopenia
    - Also important as these patients are at risk of acquired VonWillebrand disease

# Treatment

- ◆ Brief review here as covered elsewhere in this forum

# Consensus panel recommendations for initiation of therapy in WM.

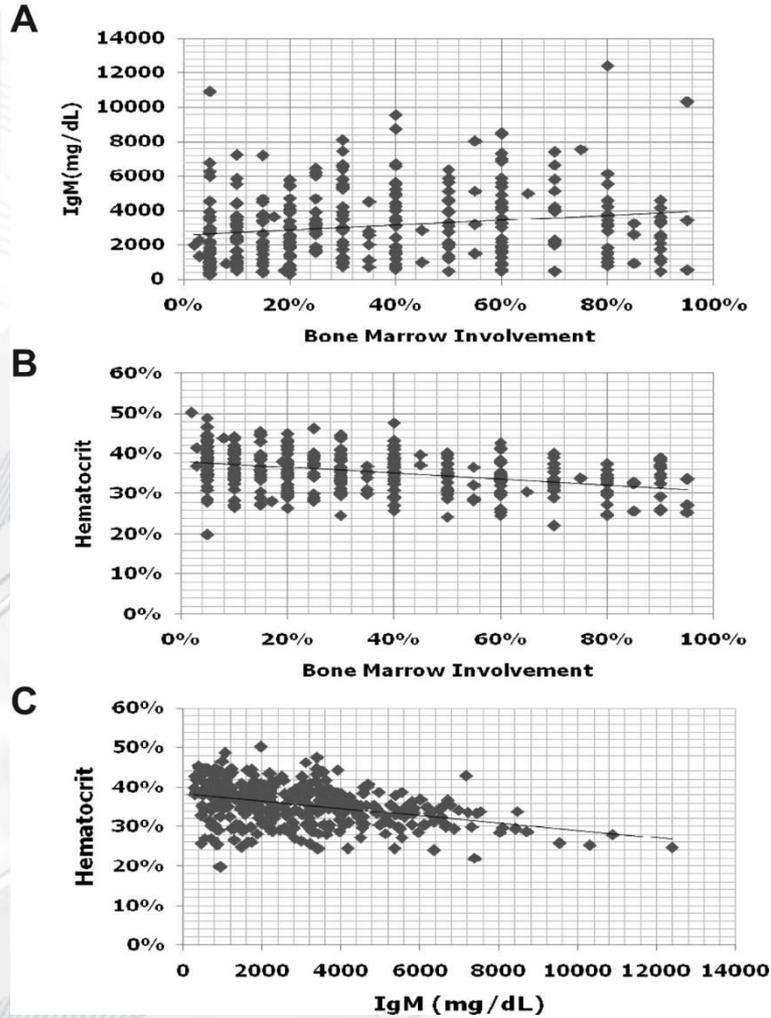
- ◆ A high IgM level is not by itself an indication to initiate therapy.
- ◆ Hematocrit <30; Platelet count <100,000.
- ◆ Alleviate symptoms attributable to WM.
- ◆ Symptomatic Hyperviscosity (>4.0 CP).
- ◆ Moderate-Severe Neuropathies.
- ◆ Symptomatic cryoglobulinemia, cold agglutinin disease.

**Semin Oncol 30: 116, 2003**

# Very important

- ◆ The level of IgM and/or the percentage of LPL (WM) cells in the bone marrow varies tremendously between WM patients
- ◆ Some patients with very low IgM levels have lots of symptoms while others with very high levels may not have symptoms at all!

Figure 1 Comparisons of serum IgM, hematocrit, and bone marrow disease involvement for 356 newly diagnosed patients with WM



Treon, S. P. Blood 2009;114:2375-2385



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# MYD88 L265P Somatic Mutation in Waldenström's Macroglobulinemia

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# Briefly

- ◆ Should all patients with WM be tested for MYD88?
- ◆ What about CXCR4?
- ◆ Some disagreement here

# Questions?

