Monoclonal Gammopathies and Associated Disorders

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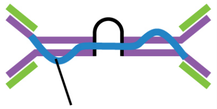
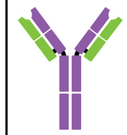
Objectives

- Understand what tests to order in workup of monoclonal gammopathies
- How to interpret common laboratory studies in monoclonal gammopathies
- Disorders associated with Monoclonal proteins

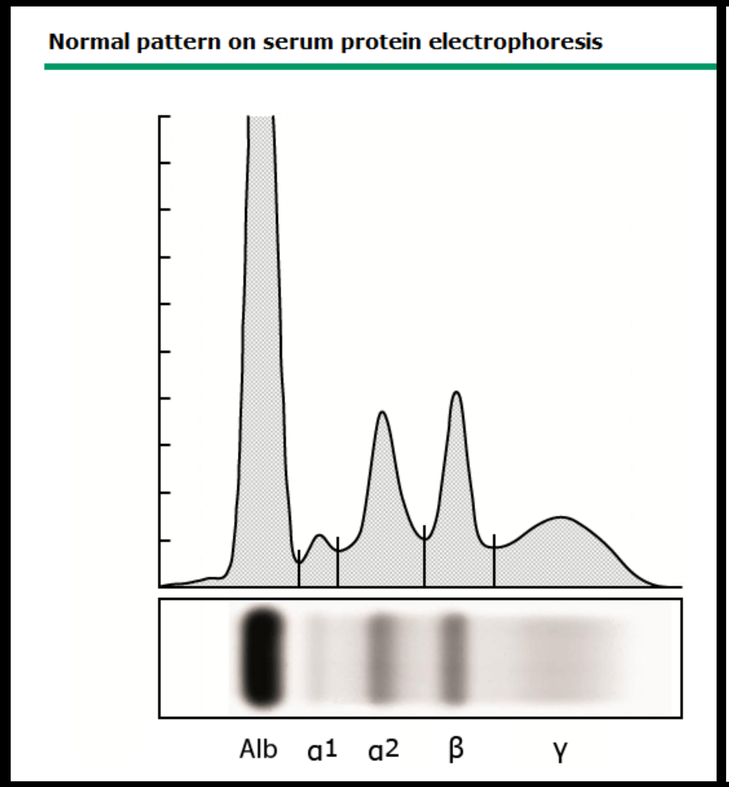
Laboratory Testing in Monoclonal Gammopathies

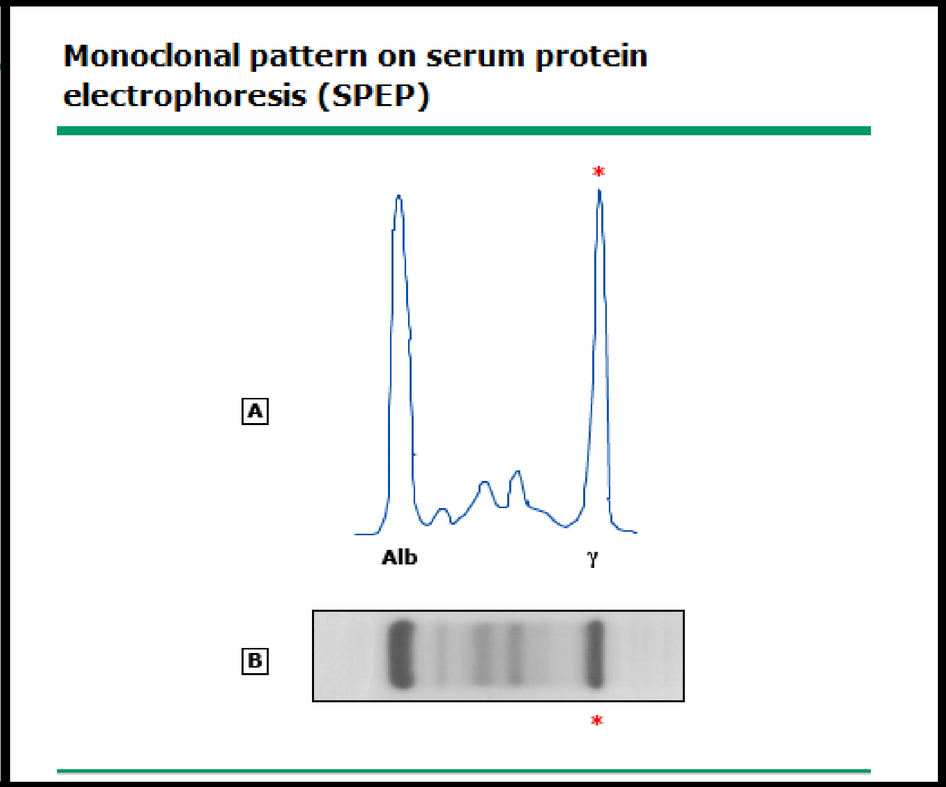
The Five Immunoglobulin (Ig) Classes					
	IgM pentamer	IgG monomer	Secretory IgA dimer	IgE monomer	IgD monomer
					
Heavy chains	μ	γ	α	ε	δ
Number of antigen binding sites	10	2	4	2	2
Molecular weight (Daltons)	900,000	150,000	385,000	200,000	180,000
Percentage of total antibody in serum	6%	80%	13%	0.002%	1%
Crosses placenta	no	yes	no	no	no
Fixes complement	yes	yes	no	no	no
Fc binds to		phagocytes		mast cells and basophils	
Function	Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor	Main blood antibody of secondary responses, neutralizes toxins, opsonization	Secreted into mucus, tears, saliva, colostrum	Antibody of allergy and antiparasitic activity	B cell receptor

- M protein - Monoclonal Ig secreted by an abnormal expanded clone of plasma cells
- M protein may be intact, or light chain or rarely heavy chain restricted
- Presence of an M protein indicates an underlying clonal plasma cell or lymphoproliferative disorder
- Clonal process may be malignant or produce a small limited premalignant clone
- Limited clone may be asymptomatic or cause disease related to potential adverse properties of the M protein

Interpretation of Tests in Monoclonal Gammopathies

- **SPEP**
- Inexpensive screening test using agarose gel electropheresis
- If M protein found - can be quantified using a densitometer tracing of gel





Polyclonal gammopathy

Liver disease – 61 percent

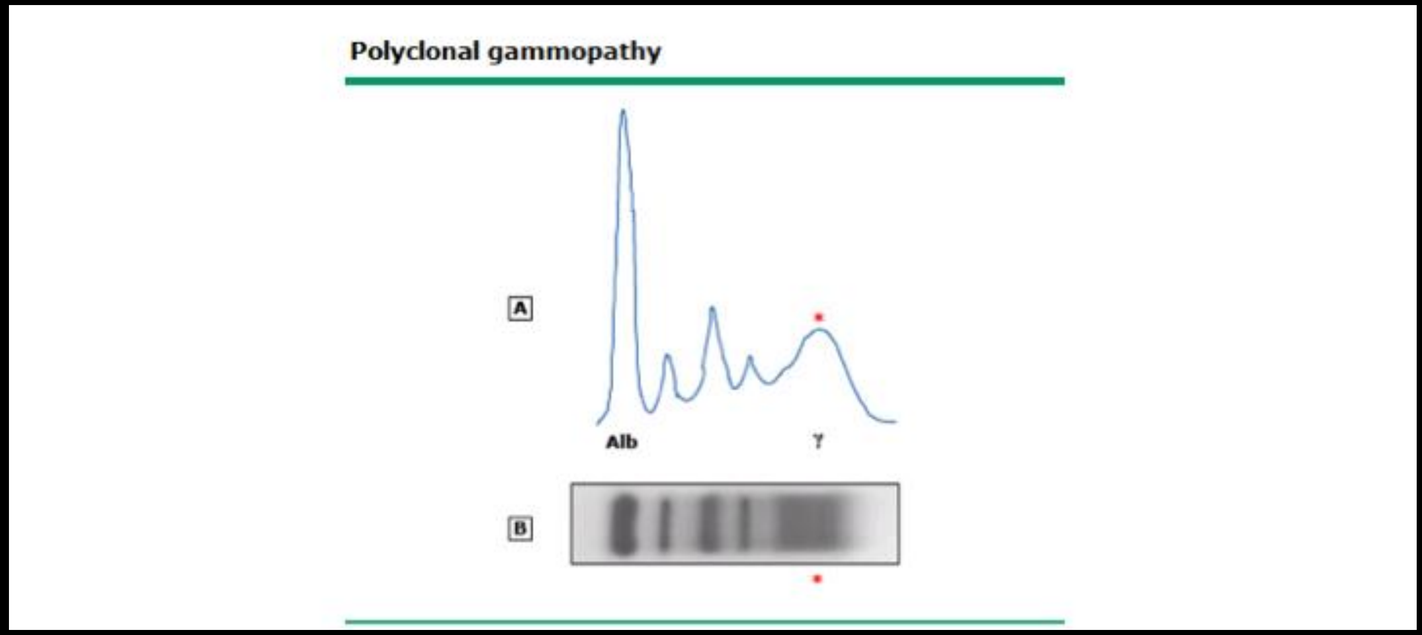
Connective tissue disease - 22 percent

Chronic infection – 6 percent

Hematologic disorders – 5 percent

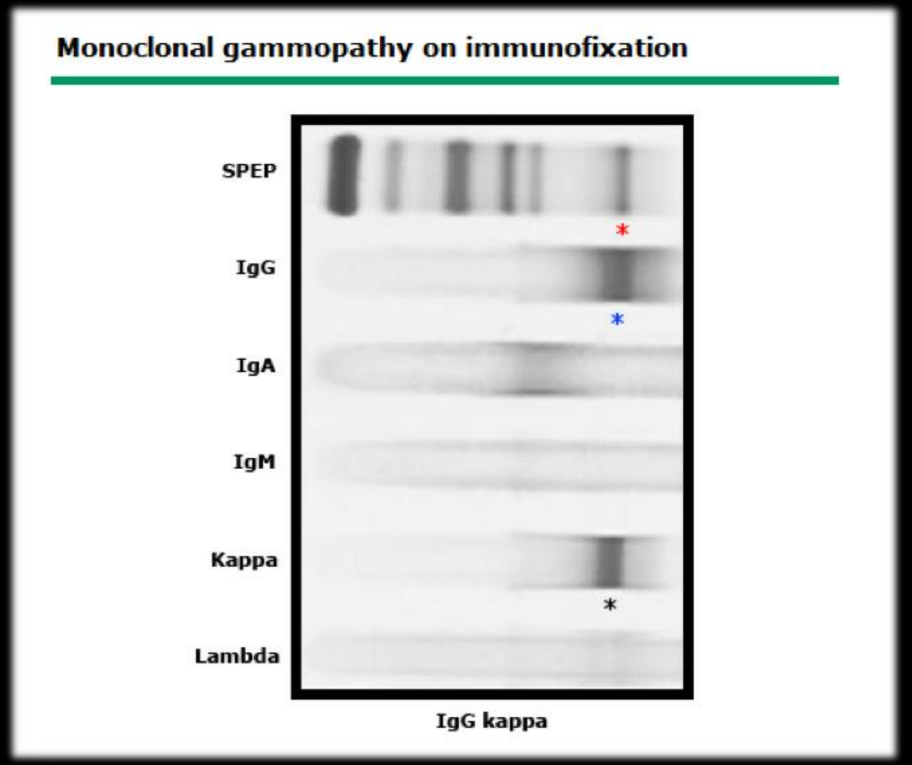
Non-hematologic malignancy – 3 percent

Other – 3 percent



Serum Immunofixation

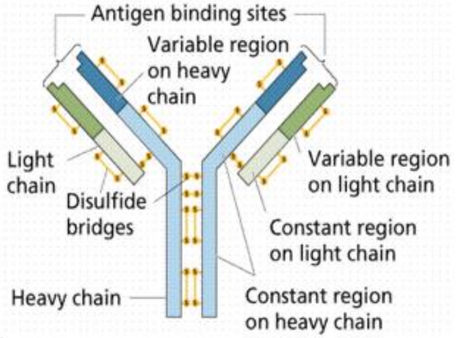
- Essential to differentiate monoclonal from polyclonal proteins
- Will detect an M protein at a concentration of at least 0.02 g/dl and a urine M protein at a concentration of >0.004 g/dl



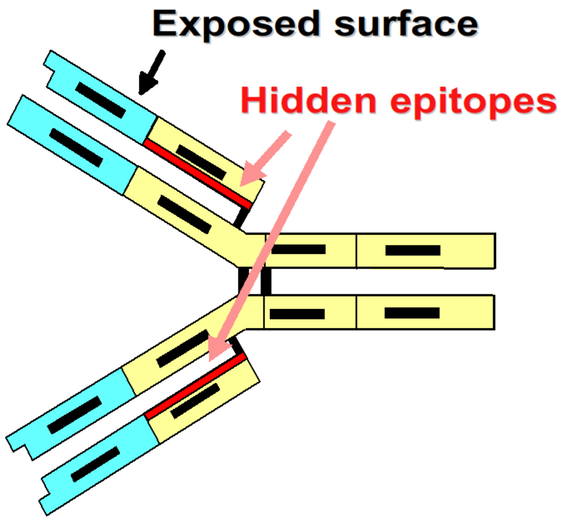
Serum Free Light Chains

Free Light Chain Physiology

- 500-1000mg of Free Light Chain Produced Daily
  - 2/3 Kappa
  - 1/3 Lambda
- Half Life
  - Kappa: 2-4 hours
  - Lambda: 3-6 hours
- Clearance
  - Proximal Tubule
  - Reticuloendothelial System

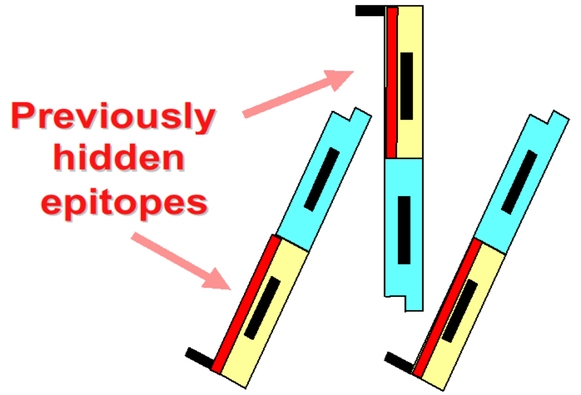


Intact Immunoglobulin



Monoclonal Gammopathies

Free Light Chain



FLC reference range:

κ 3.3–19.4 mg/L

λ 5.7–26.3 mg/L

κ/λ ratio 0.26–1.65

Serum FLC

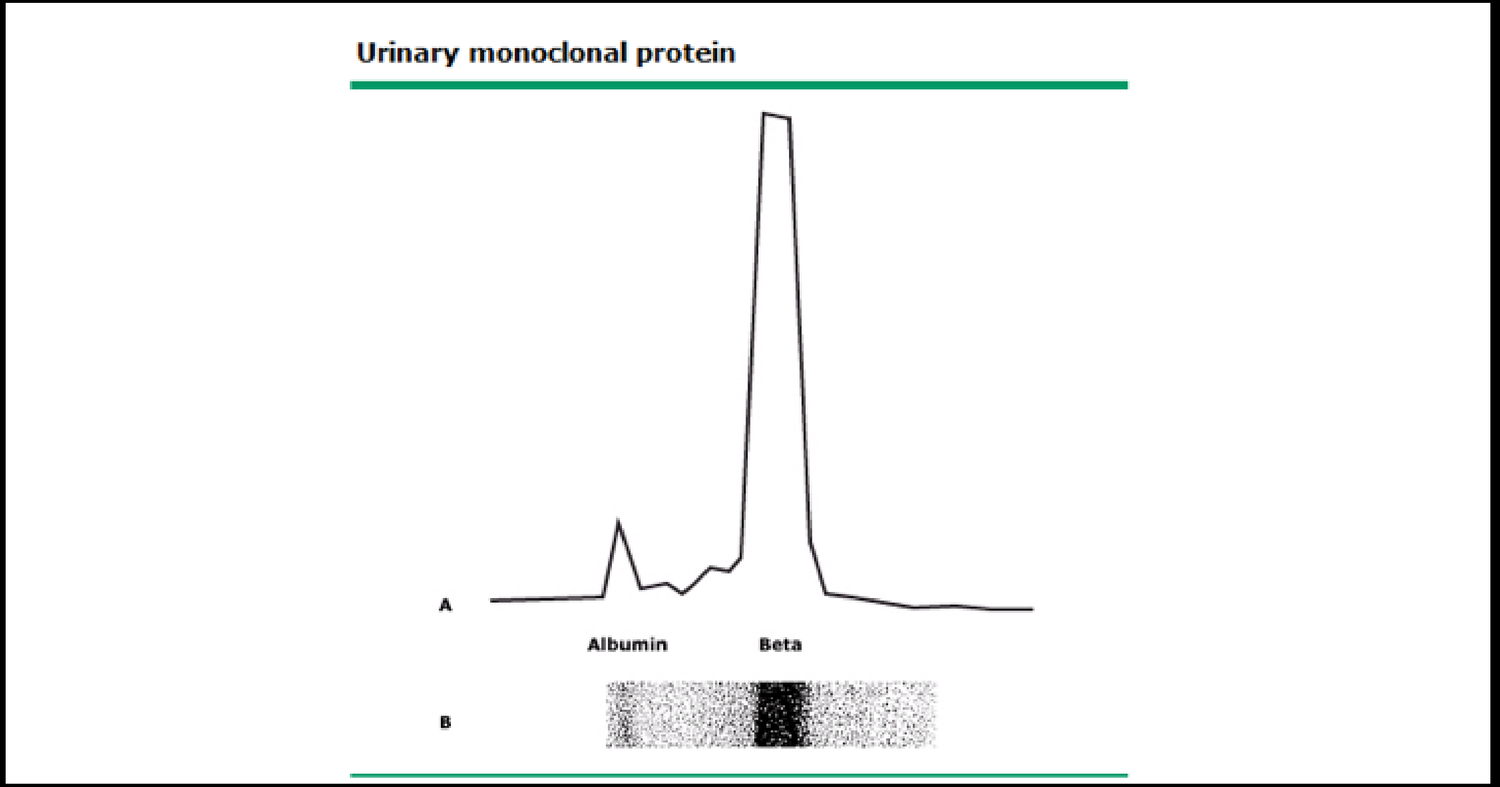
- More sensitive for detection of monoclonal light chains than urine IF
- Monitoring of patients with non secretory or oligosecretory MM
- Dx and monitoring of light chain MM and AL amyloid
- Prediction of risk of progression of MGUS, Smoldering Myeloma, solitary plasmacytoma of bone
- Diagnosis, monitoring during and after treatment and prognosis of MM
- Potentially obviates need for urine protein studies in initial evaluation of monoclonal gammopathies
- Serum FLC increase as GFR declines
- Kappa/lamda ration >3.0 unlikely due to renal insufficiency

Serum Heavylite

- Novel antibodies which identify the different light chain types of each Immunoglobulin class; IgGk,IgGL, IgAk and IgGL
- Allows accurate quantification of involved/uninvolved immunoglobulin of patients affected isotope
- Ratio of monoclonal and polyclonal Ig of the same isotype can be calculated
- HLC ratios can be used in screening,monitoring and risk stratifying of patients with monoclonal gammopathies

Urine Studies

- UPEP analogous to SPEP
- Monoclonality confirmed by urine IF
- 24 hour urine to determine total amount of protein excreted in urine per day
- Quantity of M protein determined by measuring size of M spike(%) and X by total 24 hr urine protein excretion and usually reported as g/24 hour



M Protein Disorders

- MGUS
- Multiple Myeloma
- Light chain amyloidosis
- Waldenstroms macroglobulinemia
- Others

MGUS

- A 58-year-old man with no significant medical history is found to have an elevated total protein concentration (8.1 g per deciliter) on a routine blood chemical study.
- He is asymptomatic, and his physical examination is normal.
- Serum protein electrophoresis reveals a monoclonal spike of 2.1 g per deciliter at the gamma region; immunofixation shows a monoclonal IgG kappa protein.
- What further evaluation is warranted, and assuming the diagnosis of monoclonal gammopathy of undetermined significance is made, how should the patient be followed?

MGUS

- Presence of a monoclonal protein and no features of MM or other malignant disorder
- Most common plasma cell disorder
- Prevalence increases with age
- 3.2% in persons > age 50
- 5.3% in persons > age 70
- Higher in men than women and higher in blacks than whites

Table 2. Recommended Testing in Patients with Suspected MGUS.

History and physical examination
Hemoglobin concentration
Serum calcium and creatinine concentrations
Protein studies
Total serum protein concentration and serum electrophoresis (serum monoclonal protein concentration)
24-hour urine protein excretion and urine electrophoresis (urine monoclonal protein concentration)
Serum and urine immunofixation (type of monoclonal protein)
Determination of serum free light-chain ratio (kappa and lambda free light chains)*
Examination of bone marrow aspirate†
Skeletal survey†

* This determination is not yet standard procedure but is useful in assessing prognosis.

† This is not recommended if the serum monoclonal protein concentration is below 1.5 g per deciliter.

Disease Associated with MGUS

- Hip /vertebral fractures, osteoporosis
- Hypercalcemia
- Superficial Thrombophlebitis
- Mycobacterium Infection

Disease associations with MGUS: A Population based study of 17,398 patients, Mayo Clin Proc.2009;84(8):685-693

Prognosis of MGUS

- In patients with MGUS, the actuarial risk of myeloma at 25 years of follow-up is 30% and the actual risk (when competing causes of death are taken into account) is 11%.
- A high monoclonal protein concentration, a high percentage of plasma cells in the bone marrow, an IgA monoclonal protein, and an abnormal free light-chain ratio are predictors of an increased risk of progression to multiple myeloma or other malignant plasma-cell disorder.

Smoldering Myeloma

- Defined by M Spike >3g/dl and/ or monoclonal plasma cells in bone marrow >10%
- No evidence of end organ damage(CRAB)
- Higher risk of progression to MM
- 10% per year for first 5 years, 3% per year for next 5 and 1% per year for next 10
- Standard of care generally observation although one phase III study published showing lenalidomide/dexamethasone improved OS vs observation in patients with high risk smoldering MM

Multiple Myeloma—Statistics

In 2011, it was estimated that 83,367 patients were currently living with MM in the United States[1]

Prevalence

From 2007 to 2011, new diagnoses of MM in blacks included 14.8 men and 10.5 women per 100,000 people[1]

Race

Incidence

Estimated US incidence of myeloma in 2014: >24,000 new cases per year[1]

The median age at diagnosis: 69 years[1]

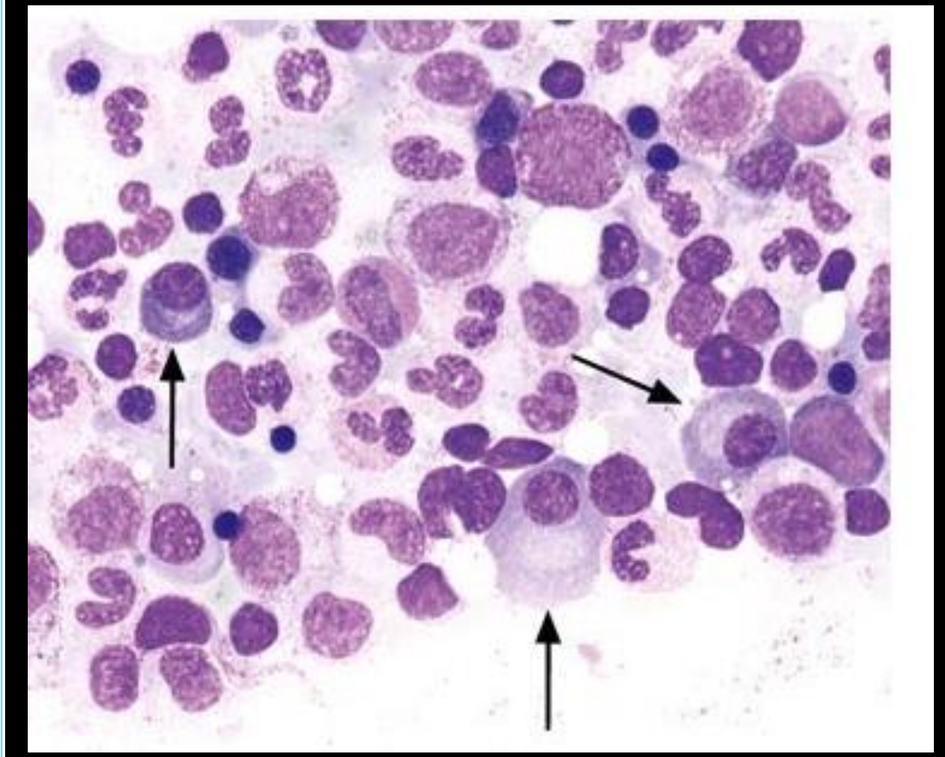
Age

Gender

From 2007 to 2011, the number of new diagnoses was 7.7 men and 4.9 women per 100,000 people[1]

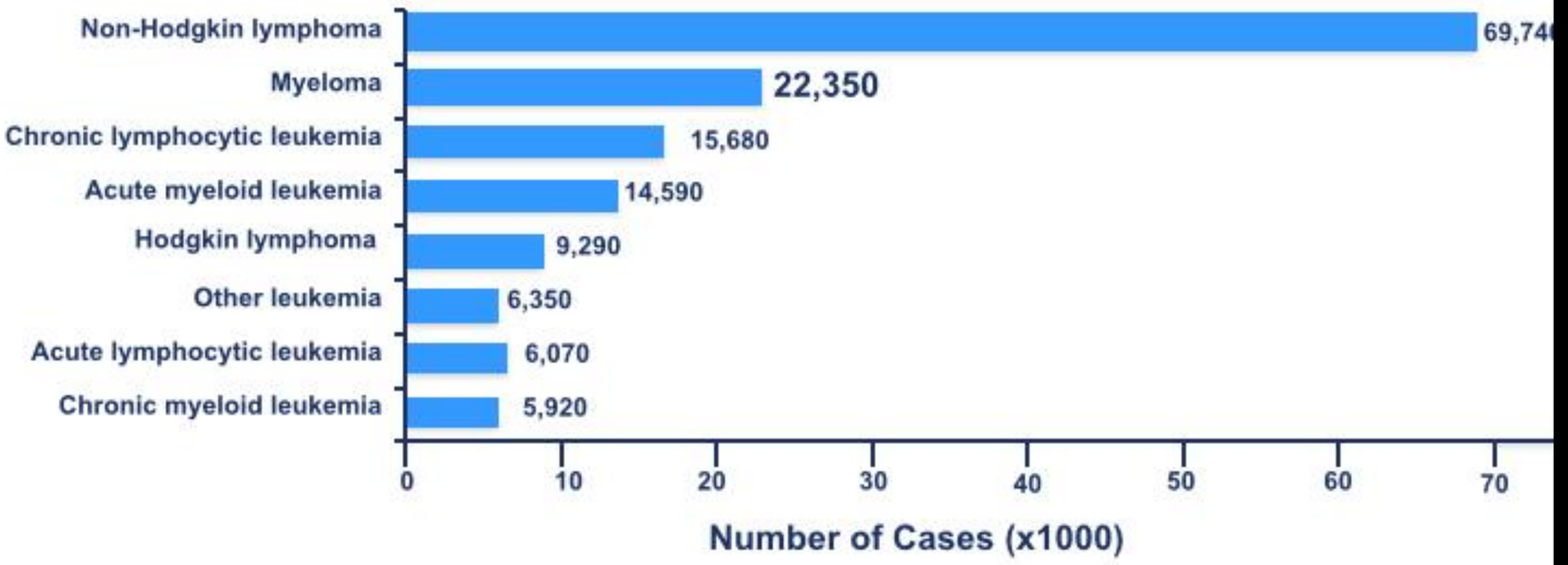
Survival

5-year survival: 44.9%[1]



Epidemiology

New Cases of Cancer in the United States (2013 estimates)[1]



American cancer society. Cancer facts and figures 2013. http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-036845.pdf. Accessed March 3, 2013.

Identification of MM

- Presence of M protein in serum or urine[1]*
- Identification of >10% monoclonal plasma cells in bone marrow[1]
- Evidence of end-organ damage: CRAB[1]

CRAB: Symptomatic MM[1-3]

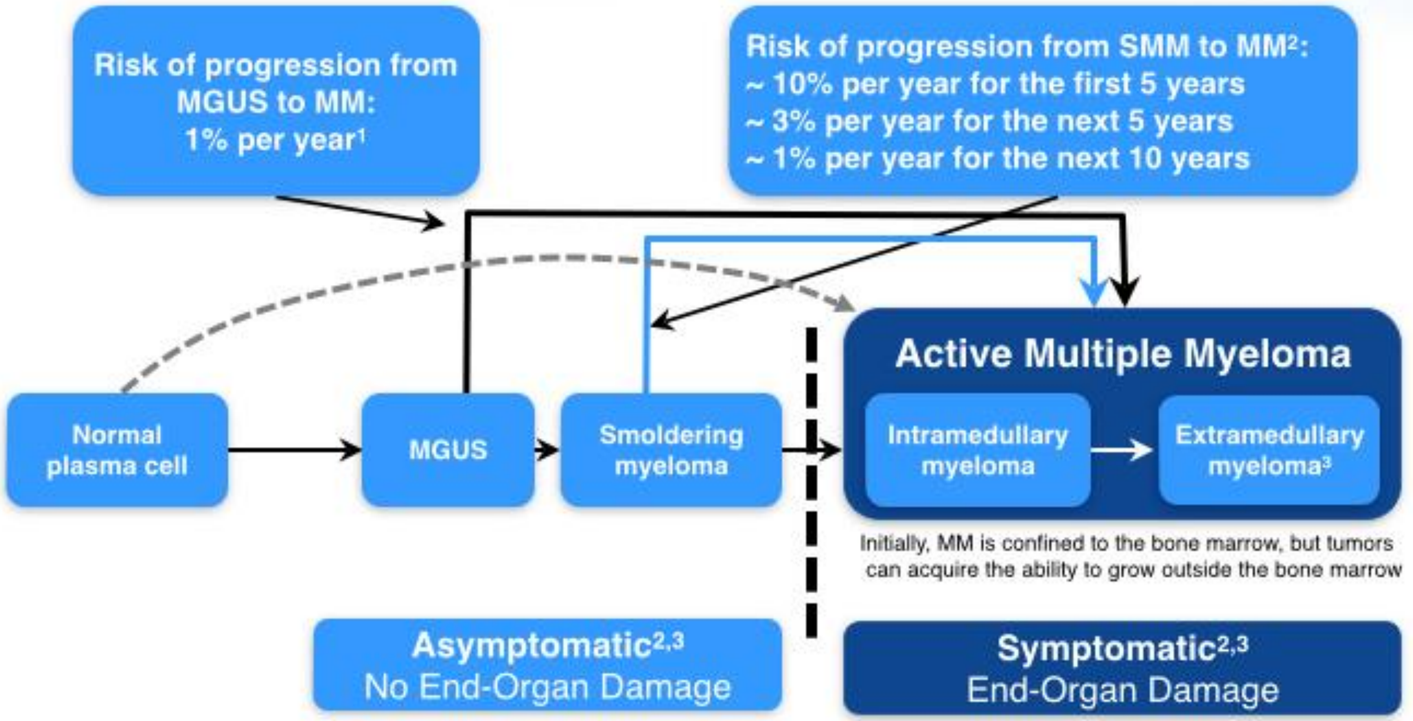
Calcium Elevation	Serum calcium ≥11.5 mg/dL
Renal Failure	Serum creatinine ≥2 mg/dL
Anemia	Hemoglobin <10 g/dL or >2 gm/dL below the lower limit of normal
Bone	Lytic lesions, pathologic fractures, or osteopenia with compression fractures

- Additionally, immune dysfunction can lead to recurrent infections in patients with MM and impaired numbers and function of B, NK, and T cells[4]

*In patients with no detectable M component, an abnormal serum FLC ratio on the serum FLC assay can substitute and satisfy this criterion.[2]

1. Kyle RA, et al. *Leukemia.* 2009;23(1):3-9. **2.** Durie BG, et al. *Leukemia.* 2006;20(9):1467-1473. 3. Kyle RA. *Hematologia.* 2010;11(1):30-39. 4. Pratt G, et al. *Br J Hematol.* 2007;138(5):563-579..

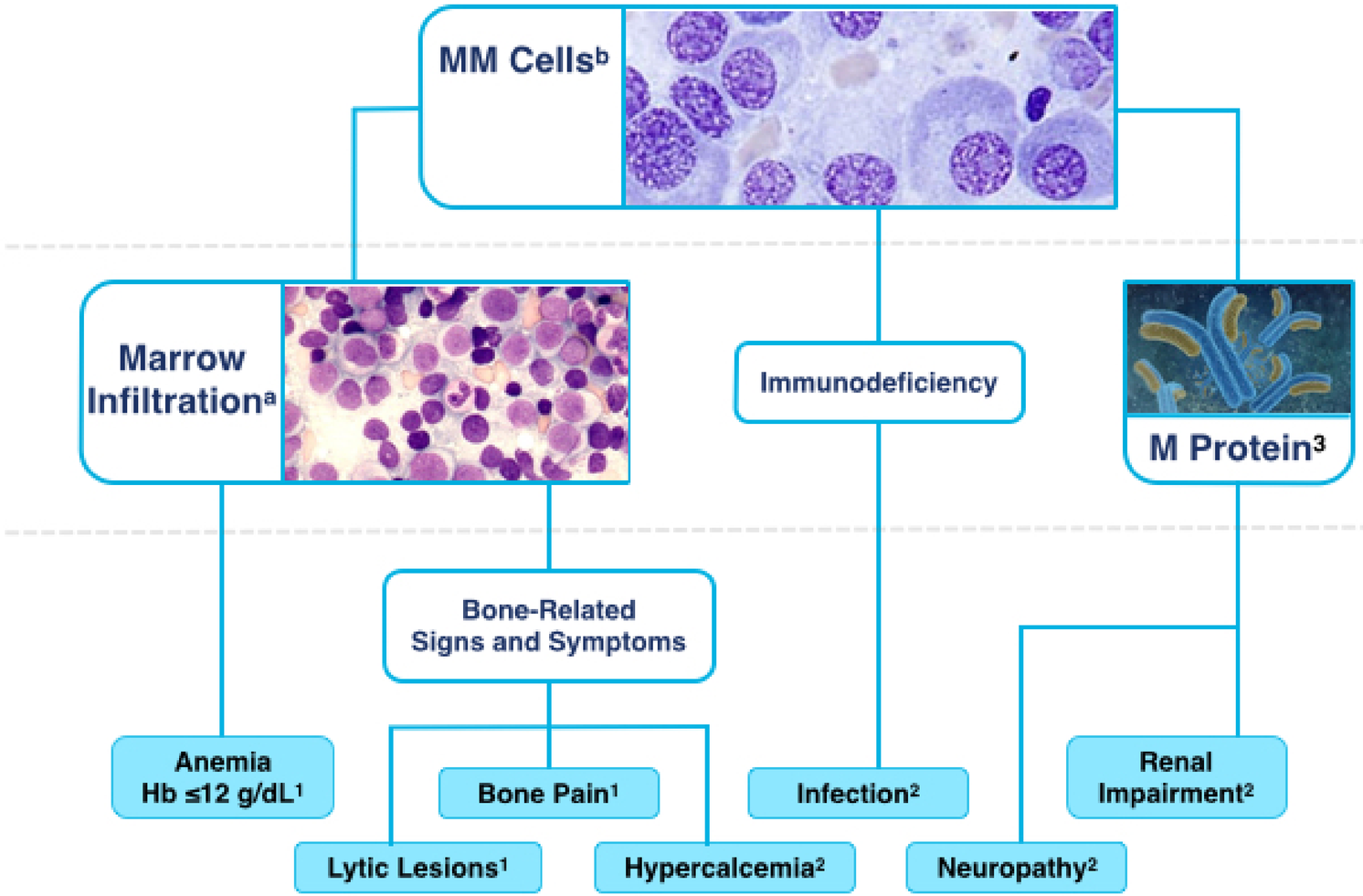
MM Disease Course



MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma.

1. Kyle RA, et al. *N Engl J Med.* 2002;346(8):564-569. **2.** McGuire TR. Multiple myeloma. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach.* 7th ed. New York, NY: McGraw-Hill; 2008:2295-2307. **3.** Kuehl MW, et al. *Nat Rev Cancer.* 2002;2(3):175-187.

Spectrum of Clinical Manifestations of MM



[a] This image was originally published in ASH Image Bank. Peter Maslak. Multiple myeloma and acute myeloid leukemia - 2. ASH Image Bank. 2011-4173. © the American Society of Hematology.

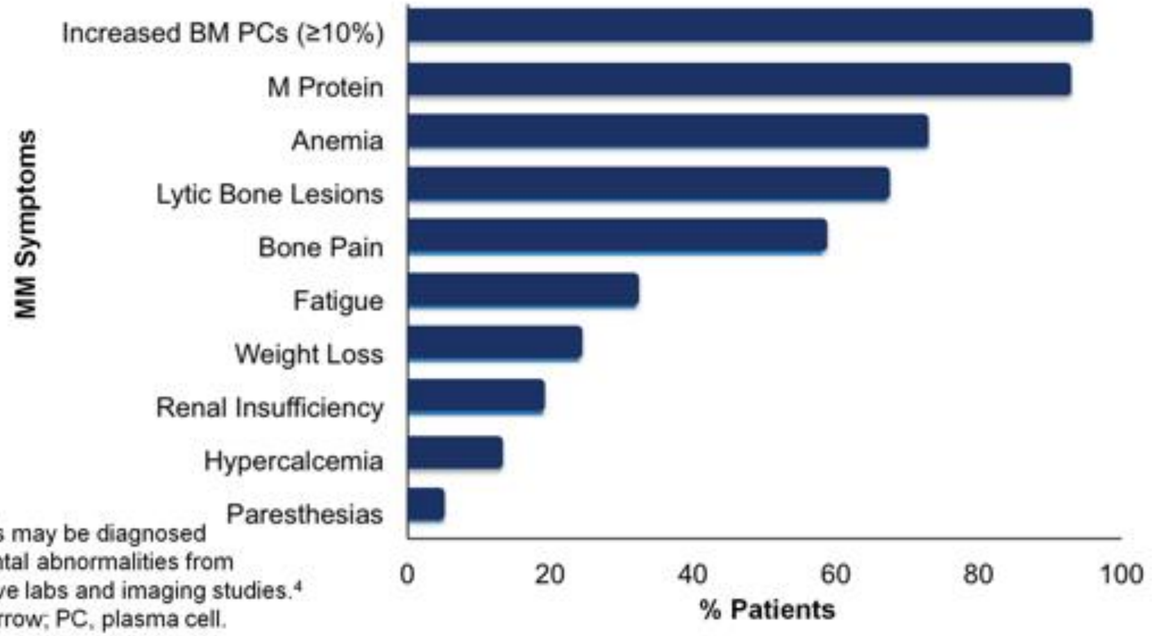
[b] This image was originally published in ASH Image Bank. Stanely Schrier. Multiple myeloma-2. ASH Image Bank. 2011-1815. © the American Society of Hematology.

1. Kyle RA, et al. *Mayo Clin Proc*. 2003;78(1):21-33. 2. Bladé J, Rosinol R. *Hematol Oncol Clin North Am*. 2007;21(6):1231-1246.
3. Ropper AH, Gorson KC. *N Engl J Med*. 1998;338(22):1601-1607.

Clinical Presentation of MM

As many as 20% of patients with MM may be asymptomatic* or exhibit mild symptoms at diagnosis[1]

Clinical Presentation of MM[2,3]

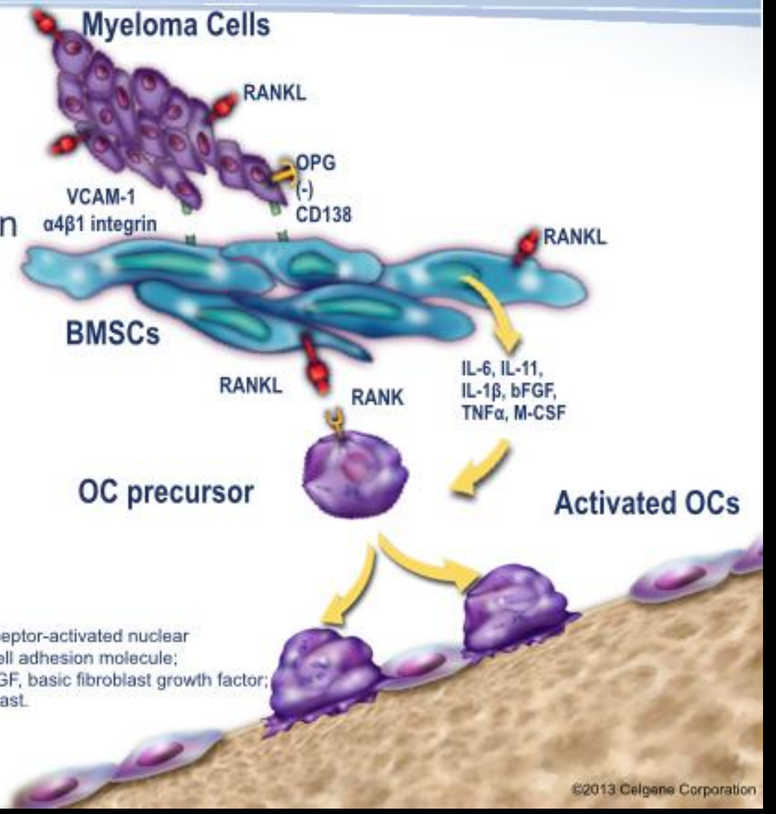


*Some patients may be diagnosed due to incidental abnormalities from comprehensive labs and imaging studies.[4]
BM, bone marrow; PC, plasma cell.

1. McGuire TR. Multiple myeloma. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 7th ed. New York, NY: McGraw-Hill; 2008:2295-2307. **2.** Kyle RA, et al. *Leukemia*. 2009;23(1):3-9. **3.** Nau KC. *Am Fam Physician*. 2008;78(7):853-859. **4.** Landgren OL, et al. JAMA;304(21):2397-2404.

Pathogenesis of Bone Disease

- Imbalance of bone remodeling
  - ⬆ Osteoclasts
  - ⬇ Osteoblasts
- Alteration of cytokine network in marrow microenvironment
  - IL-1β
  - IL-6
  - IL-11
  - TNF-α
  - RANKL

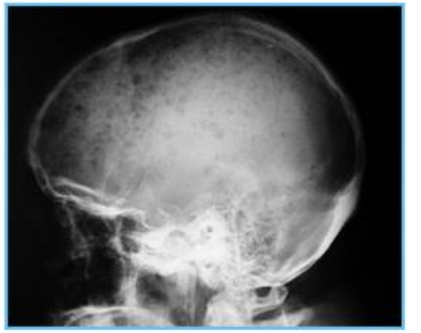


IL, interleukin; TNF-α, tumor necrosis factor-α; RANKL, receptor-activated nuclear factor-κB ligand; OPG, osteoprotegerin; VCAM, vascular cell adhesion molecule; BMSC, bone marrow derived mesenchymal stem cells; bFGF, basic fibroblast growth factor; M-CSF, macrophage colony-stimulating factor; OC, osteoclast.

Terpos E, et al. *Semin Hematol.* 2009;46(2):176-189.

Bone Complications in MM

- Bone disease present at diagnosis in over two thirds of patients[1]
  - ~80% of patients with MM will have bone involvement at some point[2]
- Can result in[3]
  - Pathologic fractures
  - Bone pain
  - Osteopenia
  - Spinal cord compression
  - Hypercalcemia
- Common sites[2,3]
  - Vertebrae
  - Sternum
  - Ribs
  - Skull



1. Tricot G. Clinical manifestations. In: Hoffman R, et al. *Hematology: Basic Principles and Practice.* 5th ed; 2008. http://www.mdconsult.com. Accessed November 6, 2012. **2.** Kyle RA, et al. *Leukemia.* 2003;78(1):21-33. **3.** Bladé J, et al. *Hematol Oncol Clin North Am.* 2006;21(6):1231-1246.

Renal disease

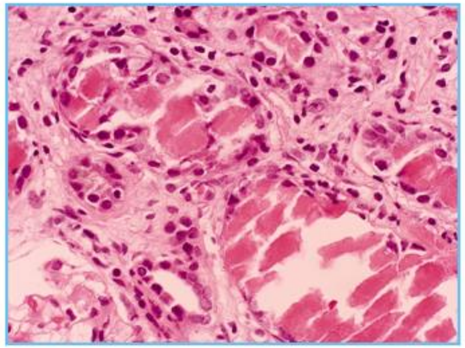
Causes of Renal Impairment in MM

- Most common cause is myeloma kidney[1]
  - Casts composed of monoclonal light chains that precipitate in the renal tubules
- Other causes that may coexist[2]
  - Fanconi syndrome (very rare)
  - Systemic amyloidosis
  - Light chain deposition disease (LCDD)
  - Hypercalcemia[1]
    - Hypercalciuria →osmotic diuresis→volume depletion→prerenal kidney failure
    - Calcium deposits→ interstitial nephritis
  - Bisphosphonate induced renal toxicity[3]

1. Tricot G. Clinical manifestations. In: Hoffman R, et al. *Hematology: Basic Principles and Practice*. 5th ed; 2008. http://www.mdconsult.com. Accessed November 6, 2012. **2.** Dimopoulos MA, et al. *Leukemia*. 2008;22(8):1485-1493. **3.** Edwards BJ, et al. *J Clin Oncol*. 29:2011 (suppl; abstr e16576).

Factors Contributing to Renal Impairment

- Dehydration[1,2]
- Advanced age[1,2]
  - Reduced GFR
- Nephrotoxic drugs and contrast agents[1,2]
- Comorbidities
  - Diabetes mellitus[3]
  - Hypertension[2]



Reversibility of Renal Failure in MM

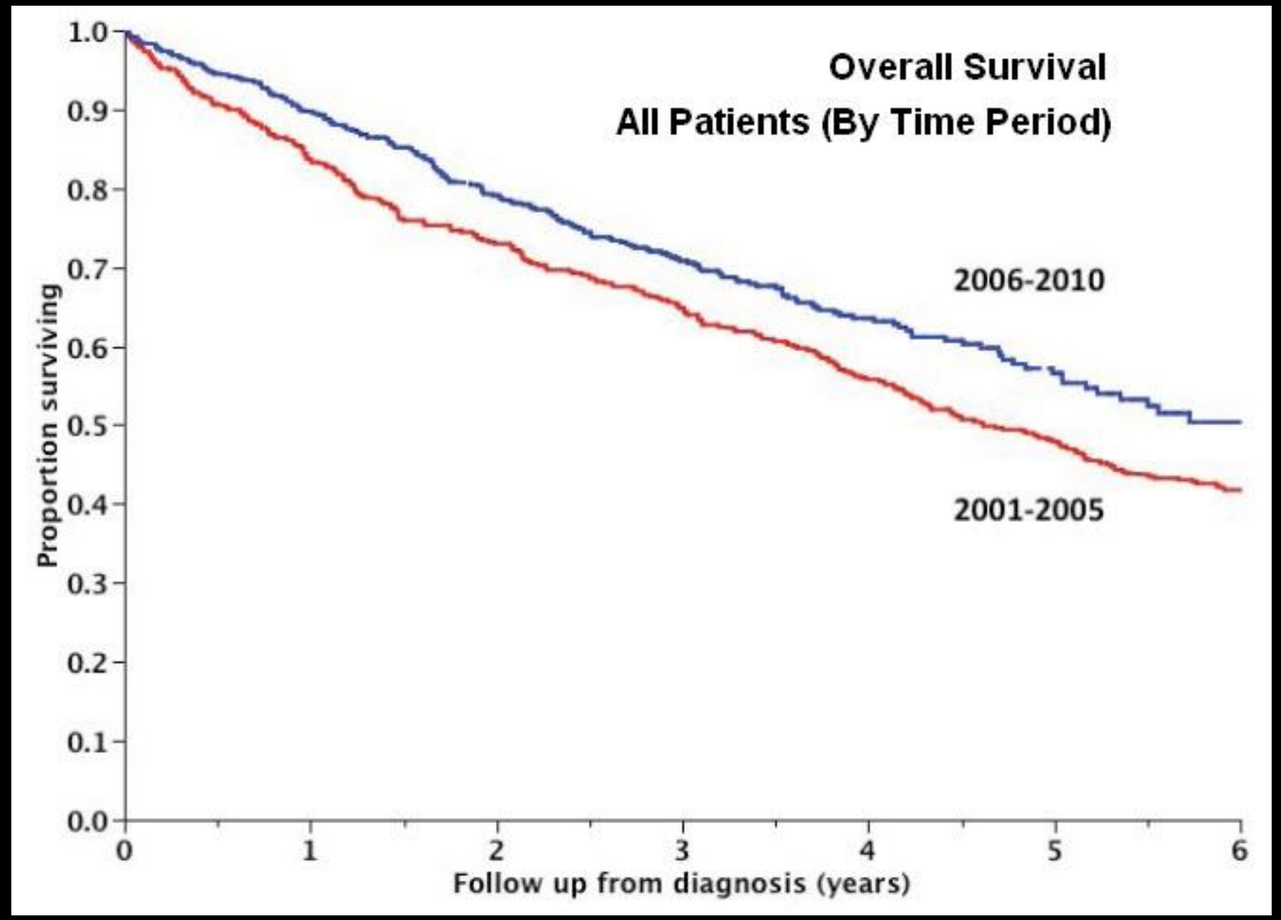
- Reversible in ~20%-60% of patients
- Approximately 50% of patients with serum creatinine <4 mg/dL will recover a normal renal function

Predictors of Reversibility[1]

- *Serum creatinine <4 mg/dL*
- *Serum calcium >11.5 mg/dL*
- *Urine protein excretion <1 g/24 h*

Prognosis and Treatment of MM

- ISS staging system,host factors, LDH, cytogenetics most important in determining prognosis
- Multiple new drugs approved over last 10 years
- IMIDS - thalidomide, lenalidomide, pomalidomide
- Proteosome inhibitors - bortezomib, carfilzomib, ixazomib
- Novel antibodies targeting cell surface proteins - CS1 and CD 38
- Chemotherapy
- Steroids

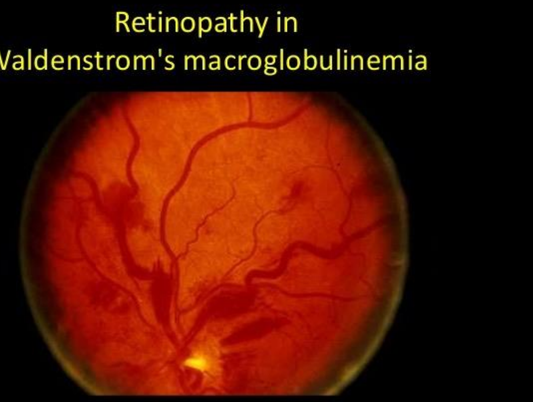


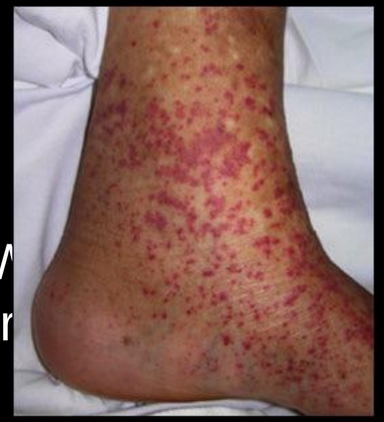
Waldenstroms Macroglobulinemia

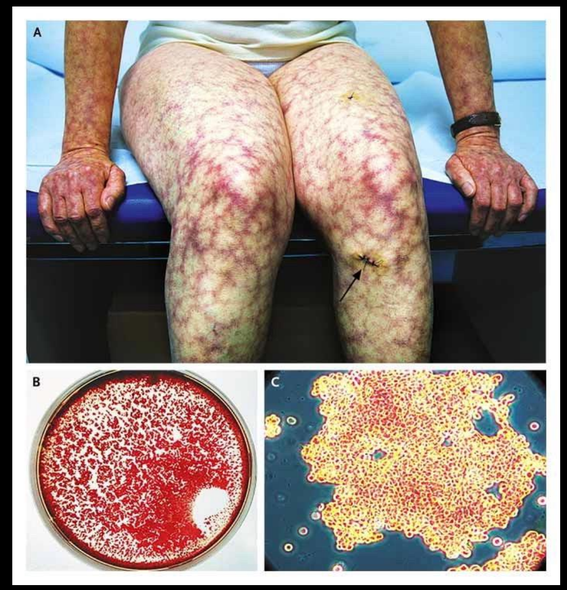
- B cell neoplasm manifested by accumulation of clonal immunoglobulin(IgM) secreting lymphoplsamacytic cells
- MYD 88 >90% of patients and CXCR4 mutations in 30-35%

Disease Manifestations

- Organ dysfunction
- Amyloid
- Hyperviscosity
- Cryoglubulinemia
- Cold agglutinins
- Peripheral neuropathy
- First new drug approved for W
  was ibrutinib - A BTK inhibitor
  2015



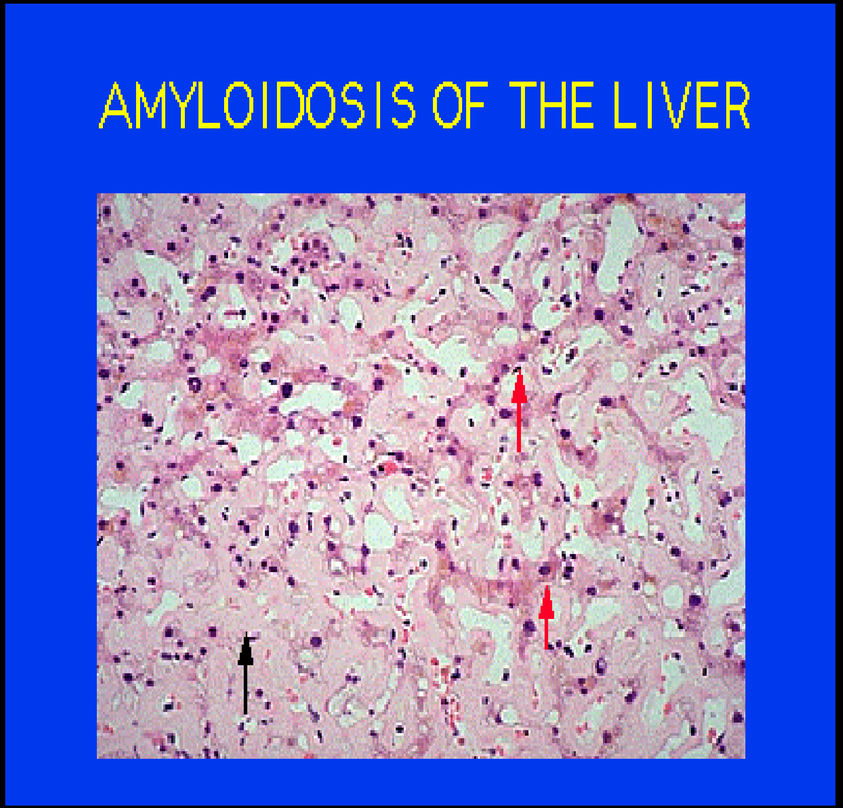




Light Chain Associated Amyloidosis

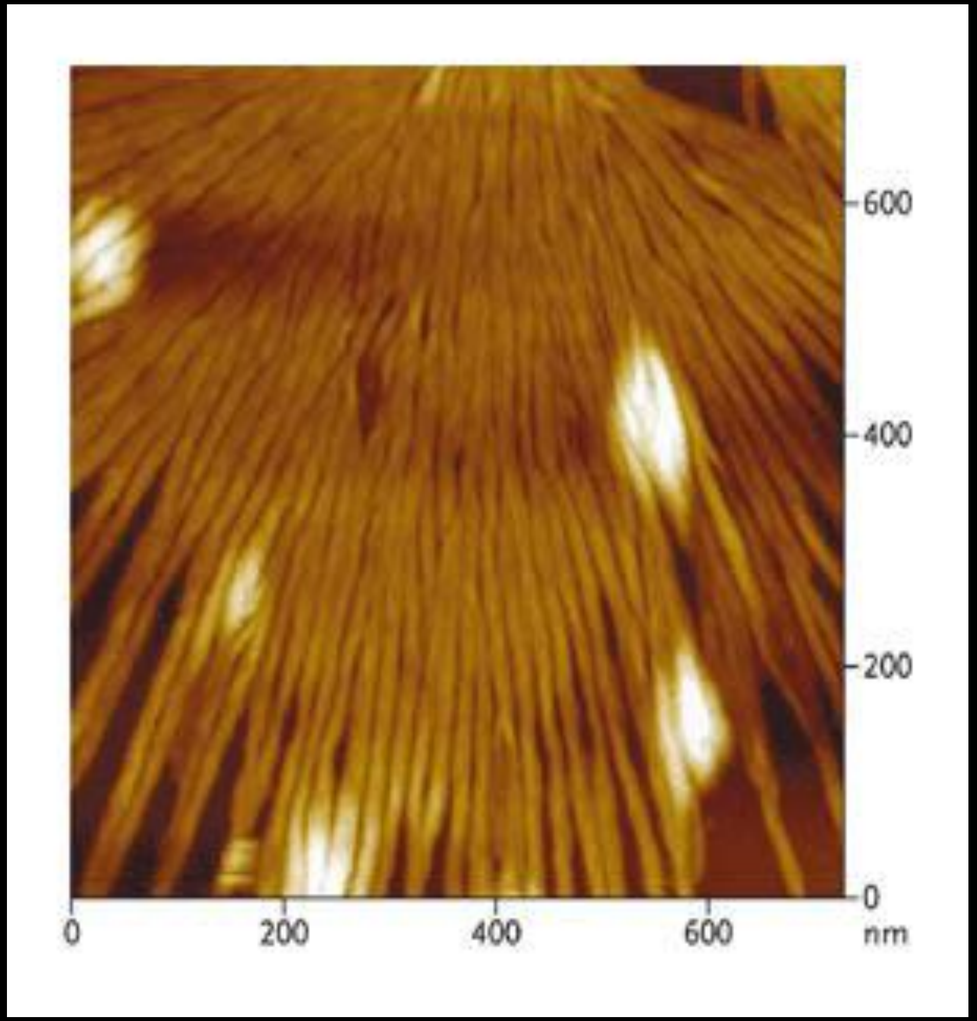
- 53 yr old white female with past medical Hx of HTN, GERD and depression presented with a 6 week history of fatigue and progressive weight loss (210-176) pounds over 4 months.
- Found to have elevated alkaline phosphatase of 1600 on routine labs and was referred for further evaluation.
- Relevant physical findings – Normal vitals except tachycardia at 100 bpm.
- 10cm liver edge felt below RCM
- Labs – WCC 9.7 HGB 14.2 Plat -568 Creatinine 0.9 Alb 3.9 Alk P – 1408 ALT 36 AST 78 Bilirubin – 1.2 TP – 8.1 gammaGT 1317 Coags normal

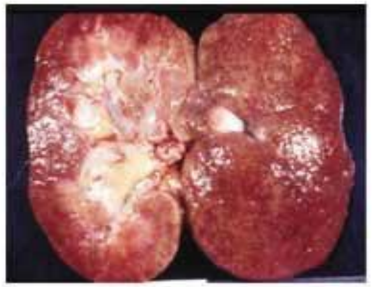
- UA: prot>300mg/dl
- 24 hour urine protein: 4485 mg/24hr
- SPEP – No monoclonal protein
- IF serum – negative
- IF urine – λ light chain
- BM biopsy – 5% plasma cells. Areas of marrow replaced by eosinophilic dense material stained by congo red.
- Liver biopsy – extensive eosinophilic dense material throughout portal tracts and lobular sinusoids.



Pathogenesis

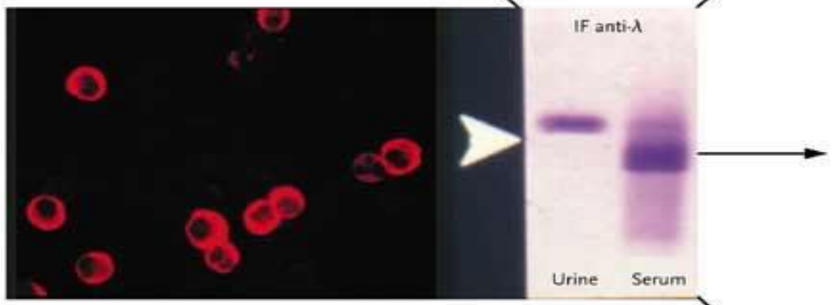
- An uncommon disorder in which proteins change conformation, aggregate and form fibrils that infiltrate organs
- Light chain amyloid derived from monoclonal B cell disorders producing amyloidgenic immunoglobulin light chains . Linear non branching aggregated fibrils with a diameter of 8-10nm and β pleated sheet conformation by xray diffraction.



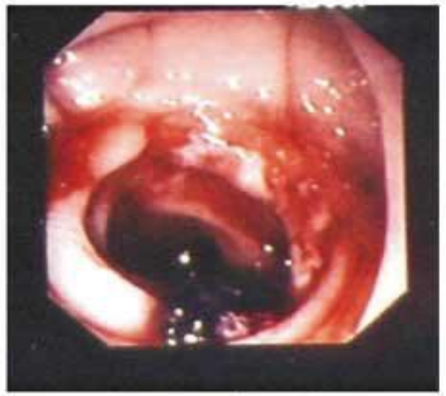


Kidney (46%)

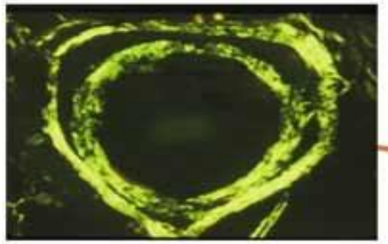
Heart (30%)

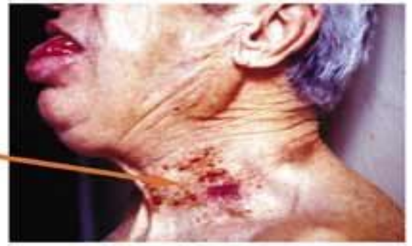


Liver (9%)



Gastrointestinal tract (7%)



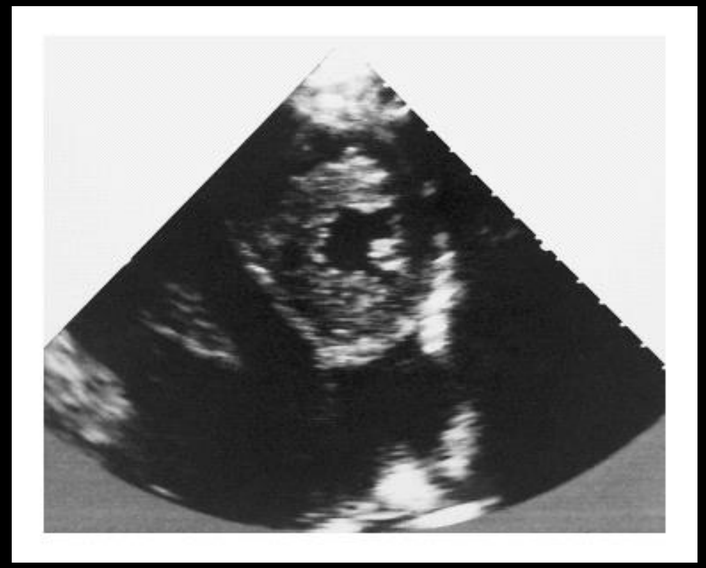


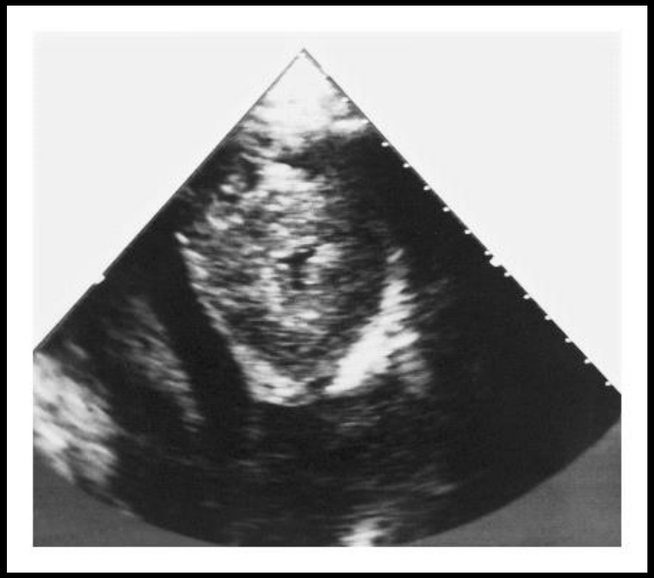
Soft tissues (3%)

Peripheral nervous system (5%)

Cardiac

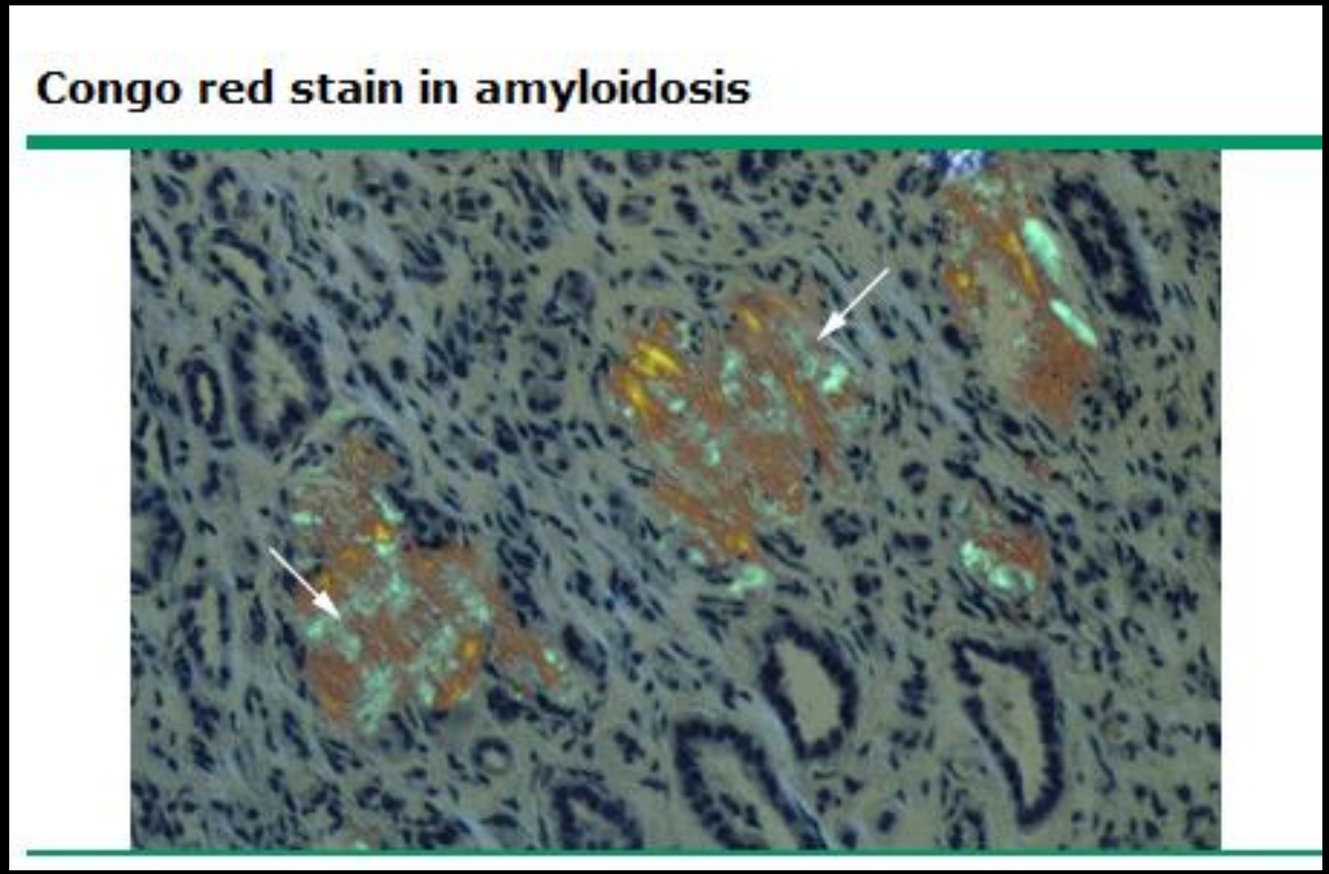
- May present with rapid and progressive onset of CHF.
- Characteristically, features are predominantly of right sided CHF.
- ECG – low voltage and may have a pattern of MI in absence of CAD.
- ECHO – concentrically thickened ventricles with normal-small cavity and diastolic dysfunction on doppler.
- Clinical clue is marked worsening of failure when CCB used.





Renal

- Nephrotic syndrome present in 30-50% at diagnosis.
- λ BJP have been associated with inferior survival as compared with κBJP or no monoclonal protein, irrespective of serum creatinine.



Gastrointestinal

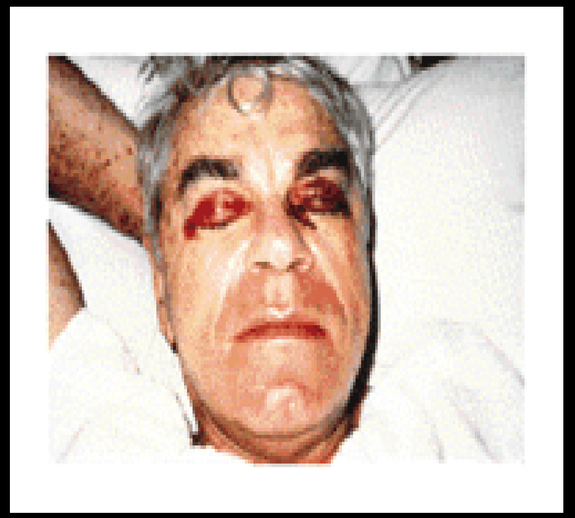
- Hepatomegaly may be striking at presentation and usually disproportionate to extent of liver enzyme abnormalities (except alkaline phosphatase which is frequently elevated).
- Presence of jaundice is an adverse prognostic factor and MST from onset of jaundice is only 3 months.
- Patients may present with severe intrahepatic cholestasis.
- Massive splenic deposition may result in functional hyposplenism.
- Amyloid can be found within any part of the GI tact and may infiltrate parenchyma, organs and nerves.

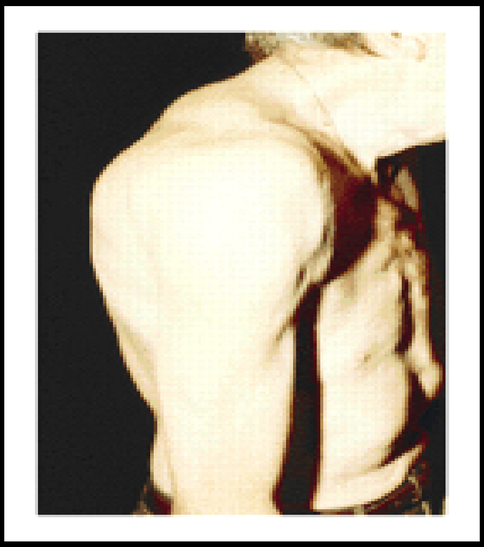
Neurologic

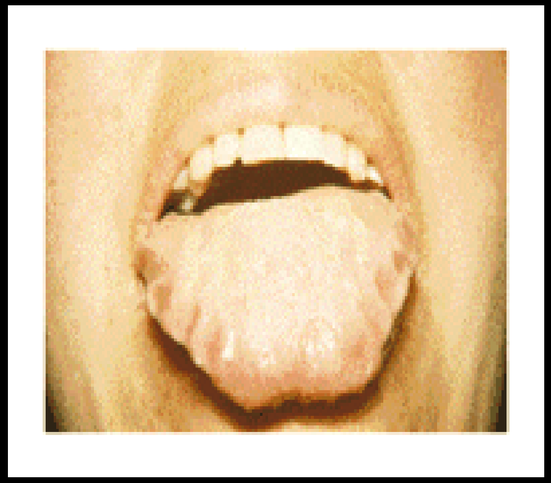
- Peripheral neuropathy may be presenting manifestation or develop subsequently durin
- Neuropathy usually distal, symmetric and progressive. Cranial nerve and autonomic ne
- Motor neuropathy rare.

- AL arthropathy – may simulate RA. Most striking appearance is the ‘shoulder pad sign’ secondary to swelling of the shoulder joints.
- Macroglossia – occurs in 10-20 %

- Vascular infiltration may result in easy bruising especially in the eyelids and flexural regions. Purpuric lesions typically occur above the nipple.
- Factor X deficiency (acquired) can occur in up to 10% of pt’s and over 2/3 of pt’s with acquired factor X deficiency have systemic Amyloidosis.







- Serious disease with high mortality.
- Overall median survival after diagnosis is < 2years in most series.
- Patients with co-existent MM have a poorer prognosis.
- Survival time largely dependent upon the organ system predominantly involved.
- Cardiac involvement is major determinant of prognosis and most common cause of death – MST from onset of CHF is 7 months.

Disorders with small clonal expansion

- Light chain associated amyloid
- LCDD
- POEMS syndrome
- Acquired falconi syndrome
- Cryoglobulinemia
- Schnitzler syndrome
- Neuropathies
- Cold agglutinin disease
- Xanthomatosis

Monoclonal Gammopathy of Renal Significance

- Renal conditions attibuted to a clonal plasma cell disorder that is more “MGUS-like” in terms of bulk and proliferative rate
- MGRS diagnosed by monoclonal deposits in kidney
- Restriction to a single class of light chain and/or heavy chain
- Monclonal protein studies should be performed to match monoclonal protein in circulation with monoclonal deposits in kidney
- Monoclonal protein studies should be performed in all patients with MGRS associated renal disorders

- Immunotactoid glomerulopathy - glomerular deposits of microtubules arranged in parallel arrays - microtubules associated with IgG most commonly - 50% of patients have lymphoma - most commonly CLL
- Type I and II cryoglobulinemic GN
- Monoclonal immunoglobulin deposition disease of the Randall type (MIDD)
- Proliferative GN with Ig deposits
- Treatment of MGRS related disorders directed to related clonal disorder

Thank you
?Questions