M-Protien, what to do next?

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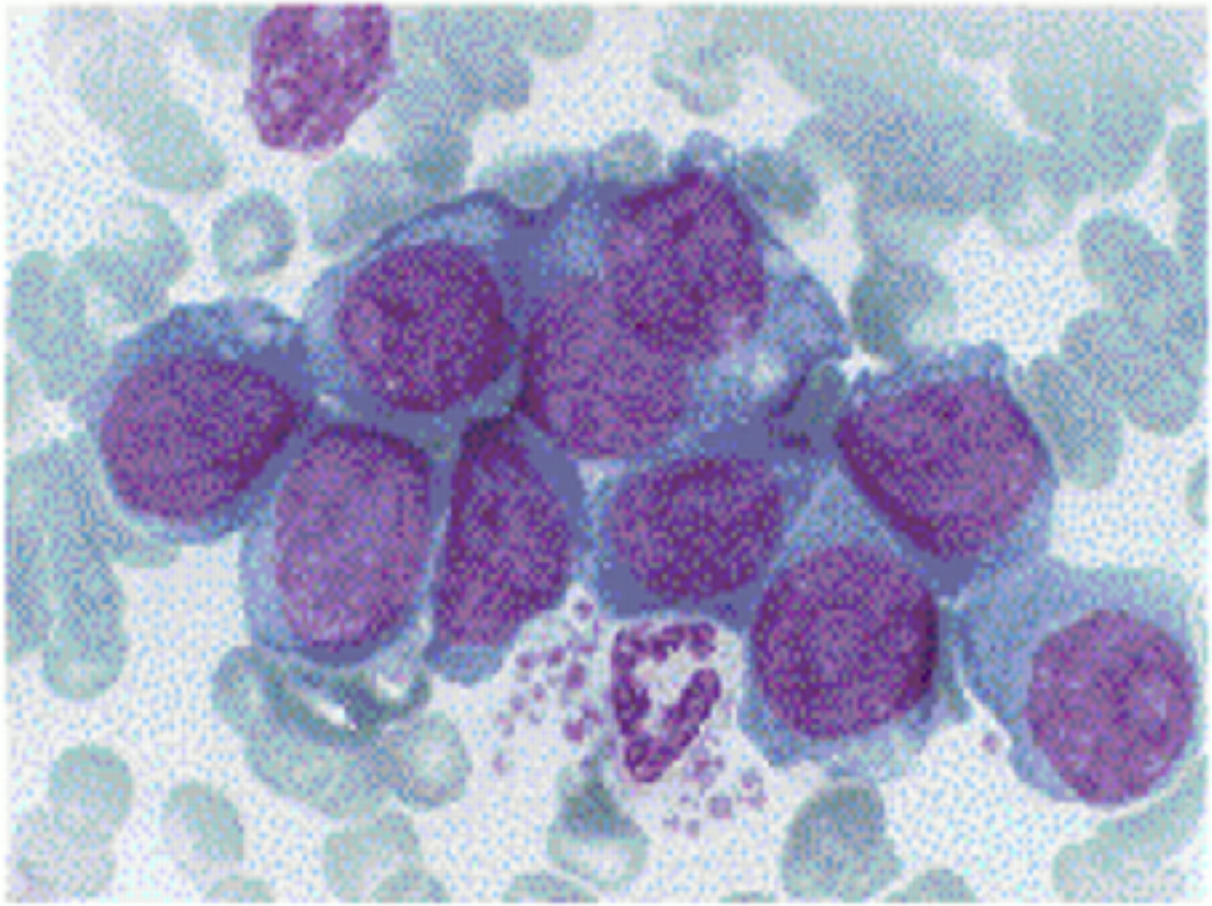
Disclosures

- Advisory Boards: AMGEN, Lundbeck, NOVARTIS

Subtypes of Plasma Cell Disorders

- Increased Plasma Cells
  - Monoclonal Gammopathy
  - Myeloma
  - Macroglobulinemia (IgM)

- Increased / Altered Products of Plasma Cells
  - Light Chain Amyloidosis
  - Light Chain Deposition Disease



Bataille, R. et al. N Engl J Med 1997;336:1657-1664

Monoclonal Gammopathy of Undetermined significance

- 61 YO M, with history of DM, HTN. Diagnosed to have carpal tunnel syndrome. No back pain, no constitutional symptoms.

Labs: HG 149, Cr 77, Ca 2.2, IgG 11, IgA 2, IgM .9 SPEP Band in the IgG Kappa region. IFE IgG Kappa M-Protien. Serum free light chain slightly elevated Free Kappa. Ratio slightly elevated.

MGUS

Denotes presence of an M-protein in a patient without a plasma cell or lymphoproliferative disorder

- M-protein < 3g/dL
- < 10% plasma cells in bone marrow
- No or small amounts of M-protein in urine
- Absence of lytic bone lesions,anemia,hypercalcemia or renal insufficiency
- No evidence of B cell lymphoproliferative disorder
- Stability of M-protein over time

MGUS

- Epidemiology

- 1 % of Adults in US.
- 3 % of Adults over age 70 years.
- 11 % of adults over age 80 years.
- 14 % of adults over age 90 year.

MGUS

MGUS can progress to monoclonal disease:

IgA or IgG

Multiple Myeloma
Primary Amyloidosis
or related plasma
cell disorder

IgM

NHL
CLL
Waldentroms
macroglobulinemia

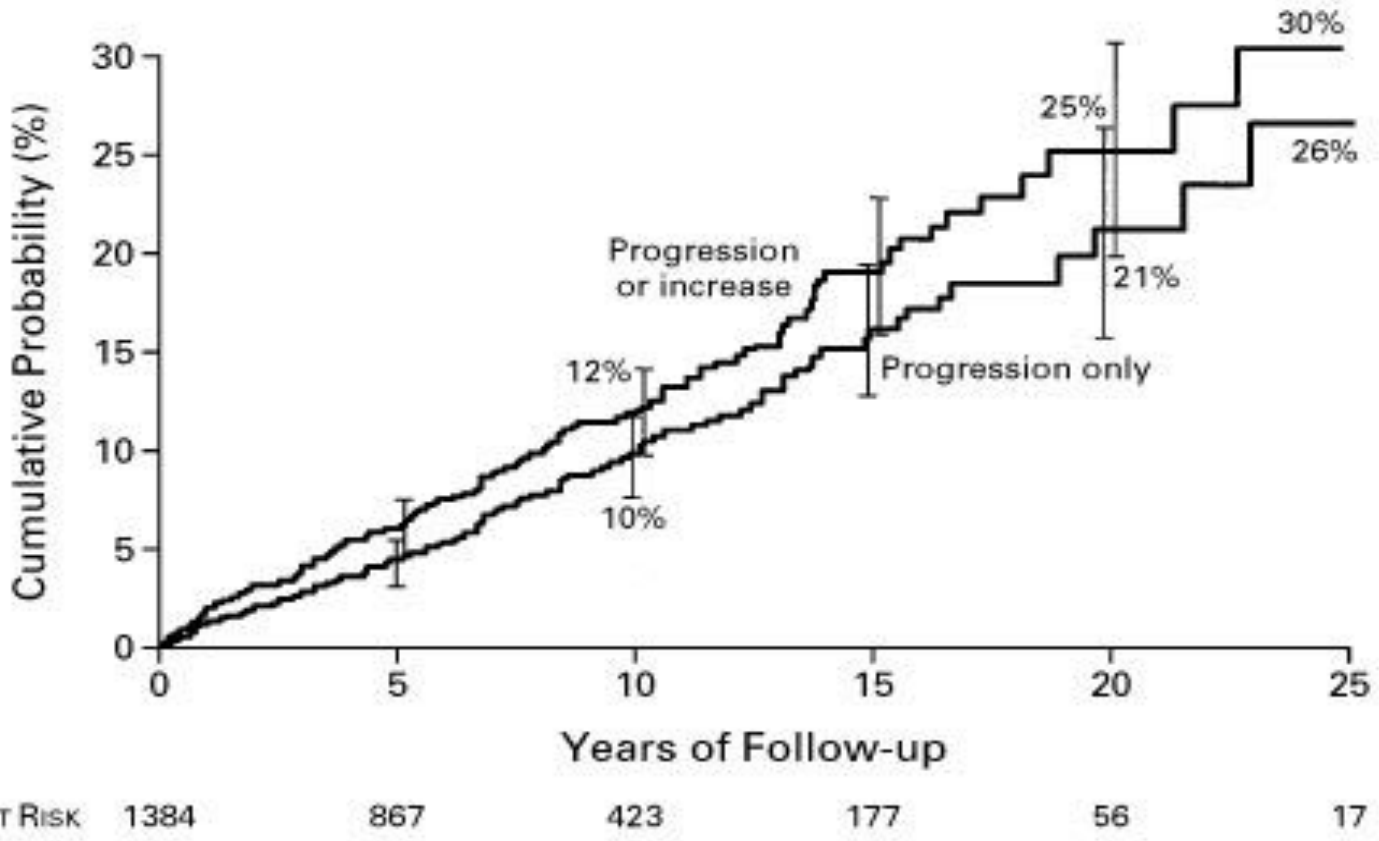
MGUS

prognosticators(predictors of progression):

1. Age
2. sex
3. Size of initial M-protein
4. Type of immunoglobulins
5. Hemoglobin
6. # of bone marrow plasma cells
7. Reduction of uninvolved imunoglobulins
8. Urinary light chains

Kyle, R. A. et al. N Engl J Med 2002;346:564-569

MGUS; risk of progression.



MGUS

Management:

- ***Periodic monitoring of serum protein electrophoresis***
- ***Interval of monitoring based on initial M-protein level***
- ***Monitoring should be at least annually LIFELONG***

- Risk does not go away with time "cumulative" probability of progression
(10% at 10 years , 25% at 25 years)

Asymptomatic MM/Smouldering MM

- 64 YO M, with chronic back pain, worse with movement. Has some fatigue, no B symptoms.
- PMH: HTN, IHD.
- Labs: Hg 121, Cr 89, Ca 2.3, IgG 26, IgA 1, IgM 0.3, Free Kappa/lambda ratio 50, SPEP shows IgG Kappa band, IFE IgG Kappa monoclonal protien.
- Skeletal survey negative.
- MRI compression fracture L2. PET can negative.
- BMB, Monocolonal Plasma cells Kappa restricted at 15%.

ASMM/SMM

- Presence of M-Protien, and elevated levels.
- No end organ damage.
- Plasma cells in the bone marrow more than 10%
- Management for these patients, would require closer monitoring, at 3 months intervals.
- Risk of progression at 25% / year.

Multiple Myeloma

- 43 YO M, presented with fatigue, epistaxis, easy bruising, diarrhea, left leg painand weight loss.
- Labs: Hg 86, WBC 4, PLT 80, Cr 110, Ca 3.2, Albumin 30, SPEP IgG Lambda, IgG 86, IgA 0.1, IgM 0.2, 24 urine IgG Lambda. PTT 57, INR 1.2.
- Skeletal survey, Lytic lesions on left Scapula, and L3, L4.
- PET scan FDG avid left scapula and spine.

Multiple Myeloma laboratory findings

- CRAB

1- Anemia: Hg < 100, or 20 drop from base line, Macrocytic, Rouleaux formation.

2- Creatinin > 177.

3- Hypercalcemia, >2.75.

4- Bone lytic lesions.

- SPEP, Heavy and light chain immunoglobulins, SFL, IFE, UPEP. B2M.
- BMB, Skeletal Survey, MRI, PET.

Multiple Myeloma laboratory findings

- SLIM CRAB\

Presence of a biomarker associated with near inevitable progression to end-organ damage –

1- ≥60 percent clonal plasma cells in the bone marrow.

2- involved/uninvolved free light chain (FLC) ratio of 100 or more (provided involved FLC level is at least 100 mg/L).

3- MRI/PET with more than one focal lesion (involving bone or bone marrow).

Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smoldering multiple myeloma

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% of biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma-defining events:

- Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
  - Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
  - Renal insufficiency: creatinine clearance <40 mL per min¶ or serum creatinine >177 µmol/L (>2 mg/dL)
  - Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
  - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT$^{\Delta}$
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage* ≥60%
  - Involved:uninvolved serum free light chain ratio$^{\diamond}$ ≥100
  - >1 focal lesions on MRI studies§

Definition of smoldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 hours and/or clonal bone marrow plasma cells 10 to 60%
- Absence of myeloma defining events or amyloidosis

Definition of monoclonal gammopathy of undetermined significance

All three criteria must be met:

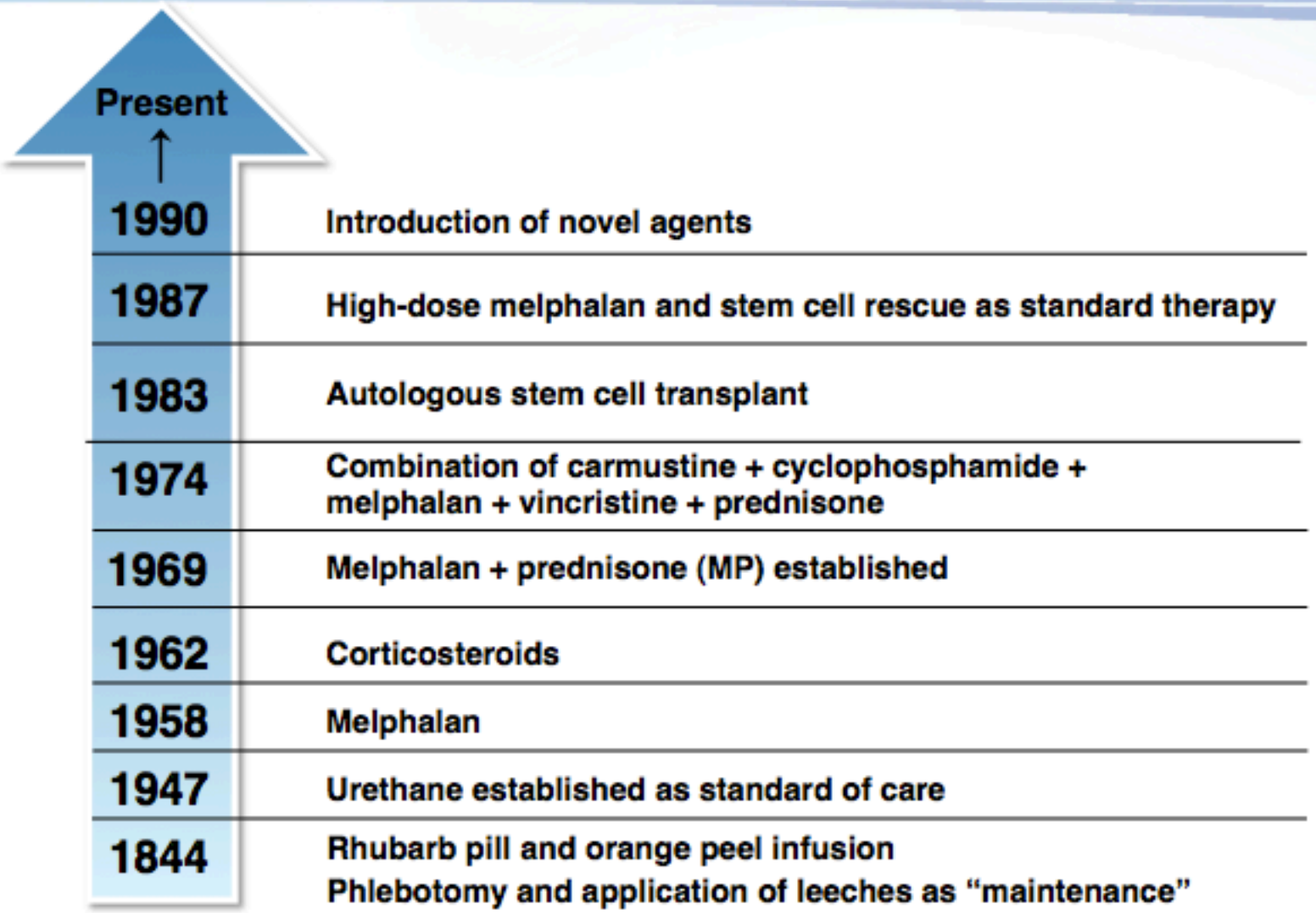
- Serum monoclonal protein <30 g/L
- Bone marrow plasma cells <10%
- Absence of myeloma defining events or amyloidosis (or Waldenström macroglobulinemia in the case of IgM MGUS)

PET-CT: ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography.
* Clonality should be established by showing kappa/lambda-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the

International Staging System

- Stage I (B2M <3.5 mg/l; Albumin ≥35)
  - Median OS 62 months
- Stage III (B2M ≥5.5 mg/l)
  - Median OS 29 months
- Stage II (Neither Stage I or III)
  - Median OS 44 months

Myeloma Treatment: A Historical Perspective



Treatment of MM

◊ **Transplant Eligible;**

Cyclophomsphamid, Bortizomib, Dexamethasone (CYBOR-D)

Re-Staging.

Stem cell collection.

High dose chemo therapy.

Autologous Stem Cell transplant.

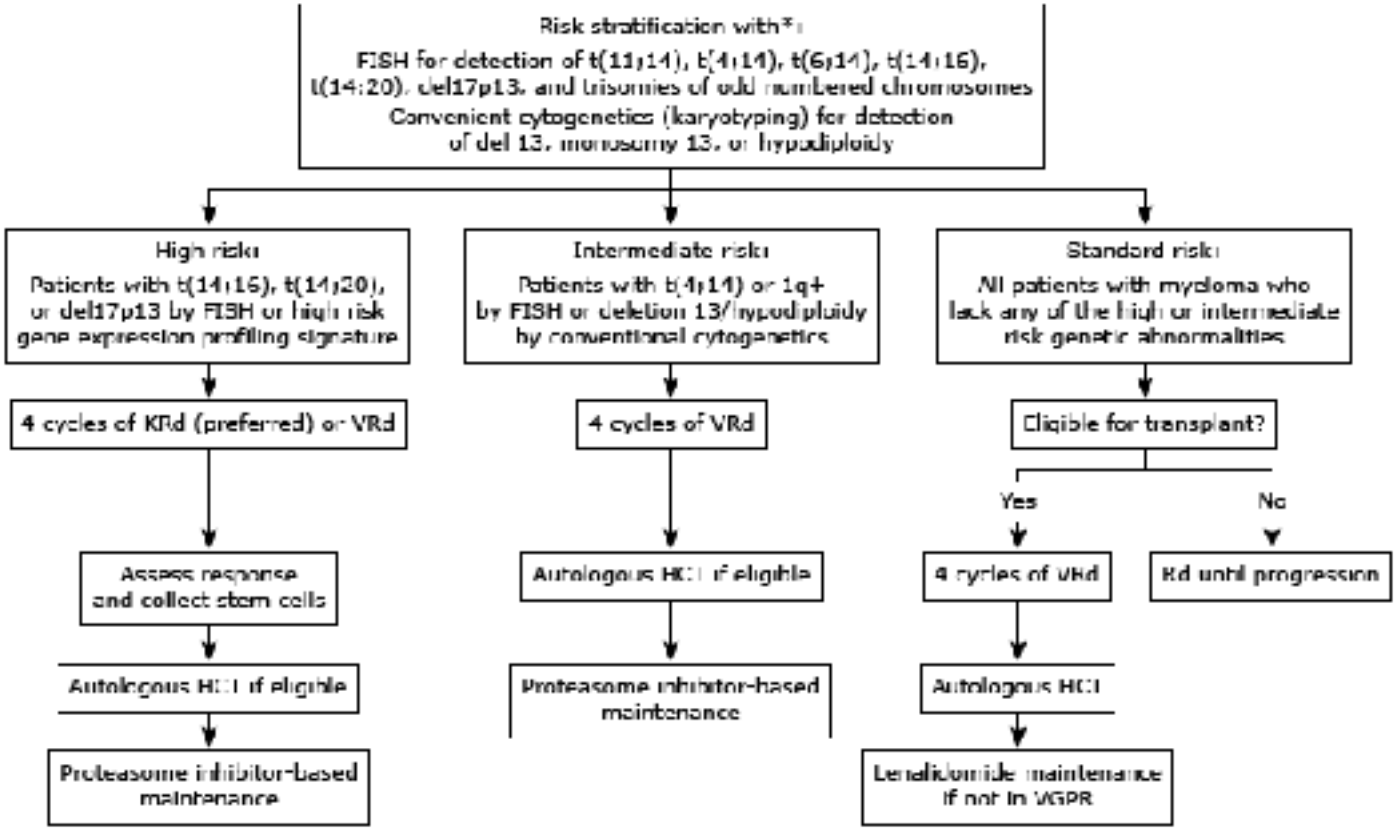
Maintenance Chemotherapy.

◊ **Transplant ineligible patients.** VMP, CYBOR-D

Relapsed Refractory MM

- ImiD (Lenalidomide, Pomalidomide)
- Second Generation Proteason inhibitors Carfilozimib.
- Immunotherapy Daratumamab.

Initial treatment of multiple myeloma by risk stratification



This algorithm illustrates our general approach to the treatment of a patient with newly diagnosed multiple myeloma. The clinician is expected to use his or her independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

FISH: fluorescence in situ hybridization; VRd: bortezomib, lenalidomide, low-dose dexamethasone; KRd: carfilzomib, lenalidomide, low dose dexamethasone; Rd: lenalidomide plus low dose dexamethasone; HCT: hematopoietic cell transplantation; VGPR: very good partial response.

* All myeloma patients are risk-stratified at initial diagnosis based on FISH studies on the bone marrow. If FISH is unavailable, conventional cytogenetics can be used as an alternative but is much less sensitive.

Diagnostic Criteria in Monoclonal Gammopathies

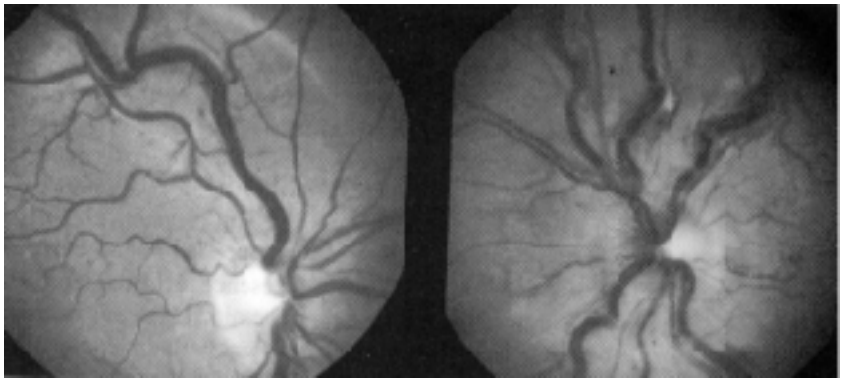
- MGUS
  - < 10% bone marrow plasma cells and M spike < 3 g/dl
  - Monoclonal protein / clonal plasma cell population
  - No End organ damage
- Myeloma
  - > 10% marrow plasma cells
  - End Organ Damage
- Indolent / Smoldering Myeloma
  - > 10% marrow plasma cells or M spike > 3 g/dl
  - No End organ damage

Waldenström Macroglobulinemia

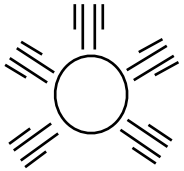
- Uncontrolled proliferation of lymphoplasmacytes producing IgM
- Median age 63 years
- Presents with weakness, fatigue, epistaxis, blurred vision
- Bone pain and lytic bone lesions are uncommon (<5%)
- 25% have hepatomegaly, splenomegaly and lymphadenopathy
- Hyperviscosity is common.

Hyperviscosity syndrome

- **bleeding (nasal and gums)**
- **blurred vision**
- **dizziness, headaches, ataxia**
- **congestive heart failure**
- **retinal vein engorgement, and papilledema**
- **rarely occurs with serum viscosity <4 centipoises (cp) (normal 1.8 cp)**



IgM pentamer



Macroglobulinemia: Principles of Therapy

- Observation in patients with asymptomatic disease.
- Active drugs for therapy
  - Alkylating agents: Chlorambucil, Cytoxan, Bendamustin.
  - MAbs: Rituxan
  - Purine analogues: Fludarabine, Cladribine
  - Bendamustine
  - Steroids
  - Bortezomib
  - Thalidomide analogues

AL Amyloidosis

- Diagnostic criteria for AL amyloidosis require the presence of **all** of the following four criteria:

●Presence of an amyloid-related systemic syndrome (eg, renal, liver, heart, gastrointestinal tract or peripheral nerve involvement).

●Positive amyloid staining by Congo red in any tissue (eg, fat aspirate, bone marrow or organ biopsy) or the presence of amyloid fibrils on electron microscopy.

●Evidence that the amyloid is light chain-related established by direct examination of the amyloid using spectrometry-based proteomic analysis or immunoelectron microscopy.

●Evidence of a monoclonal plasma cell proliferative disorder

AL Amyloid Should Be Suspected In Pts With Monoclonal Ig

- Congestive Heart Failure
- Neuropathy (including autonomic neuropathy)
- Nephrotic syndrome, Renal Failure
- Malabsorption
- Hepatosplenomegaly
- Carpal tunnel syndrome
- Macroglossia
- Unexplained constitutional symptoms

Prognostic factors

- Physiologic age ≤70 years
- Troponin T <0.06 ng/mL
- NT-proBNP <5000 ng/L
- Creatinine clearance ≥30 mL/min (unless on chronic stable dialysis)
- Eastern Cooperative Oncology Group (ECOG) performance status ≤2
- New York Heart Association functional status Class I or II
- No more than two organs significantly involved (liver, heart, kidney, or autonomic nerve)
- No large pleural effusions
- No dependency on oxygen therapy

Principles of Management in AL Amyloid

Therapy directed at the underlying clonal plasma cells.

- Melphalan
- Steroids
- Proteasome Inhibitors (Bortizomib)
- Thalidomide/lenalidomide

Disease	Distinctive Feature
Plasma Cell Leukemia[1]	Circulating plasma cells (PC) > 2,000/uL if the leukocyte count exceeds 10,000/uL or 20% PC with lower leukocyte levels
Solitary Plasmacytoma[2]	Solitary bone or soft tissue lesion with evidence of clonal plasma cells, normal BM with no evidence of clonal plasma cells, normal skeletal survey, absence of end-organ damage
Waldenström's Macroglobulinemia[3]	Lymphoplasmacytic lymphoma with bone marrow involvement and IgM monoclonal gammopathy of any concentration
Light Chain Deposition Disease[4]	Characterized by deposition of monoclonal, amorphous light chains, predominantly kappa light chains. Histologic appearance can mimic AL-amyloidosis, However, unlike AL amyloidosis, LCDD deposits do not have affinity for Congo red stain. Immunofluorescence of the bone marrow usually demonstrates a monoclonal population of plasma cells
Heavy Chain Disease[5]	M protein with an incomplete heavy chain lacking a light chain
Systemic AL Amyloidosis[5]	Presence of an amyloid-related systemic syndrome, positive amyloid staining by Congo red or EM in any tissue, clear evidence that amyloid is light chain-related established by direct sub-typing of amyloid deposits, and evidence of a monoclonal plasma cell proliferative disorder

Conclusion

- Plasma cell dyscrasias are a heterogeneous group of disorders.
- Clinical presentation may be due to the clone itself or the properties of the secreted Ig.
- Therapy largely directed (if indicated) at reducing the underlying clone.

- Questions