AMYLOIDOSIS

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Disclosures for Ann McNeill

- Consultant / Advisor for Celgene Corporation and Millennium Pharmaceuticals
- Speaker's Bureau for Celgen Corporation, Millennium Pharmaceuticals and Onyx Pharmaceuticals

Learning Objectives

- Understand the epidemiology of amyloidosis
- Describe the clinical presentation of patients with amyloidosis
- Identify the pathophysiologic mechanisms involved in amyloidosis
- Delineate treatment options for amyloidosis and the efficacy of each

Incidence and Prevalence

- "Rare" disease: each year, about 50,000 people worldwide will be diagnosed
- More than 3,000 cases diagnosed each year in North America
- 2:1 ratio of males to females
- Peaks between the ages of 60 and 67; only 1% are under age 40 in the U.S.

Rosenzweig and Landau *Journal of Hematology & Oncology* 2011, 4:47

Definition

- Amyloidosis is a rare, systemic disorder of protein metabolism
- Progressive, extracellular deposition of insoluble fibrillary protein
- Disorganization of tissue architecture
- Organ dysfunction
- Death – particularly as a result of cardiac involvement

Chaulagain & Comenzo *Curr Hematol Malig Rep* 2013 8: 291-298

WHAT IS THE ORIGIN OF THIS ABNORMAL PROTEIN?

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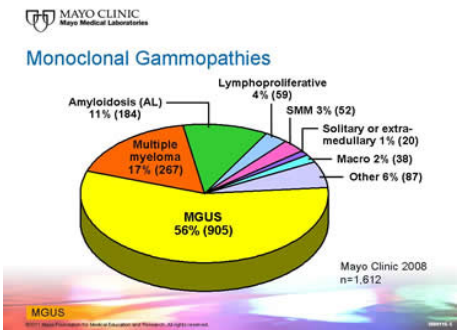
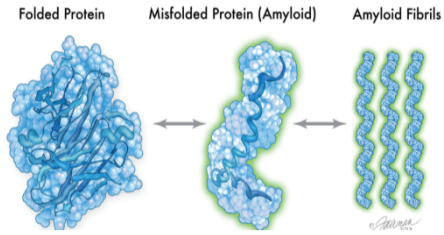
Distribution of Monoclonal Gammopathies



Pathophysiology of Amyloidosis

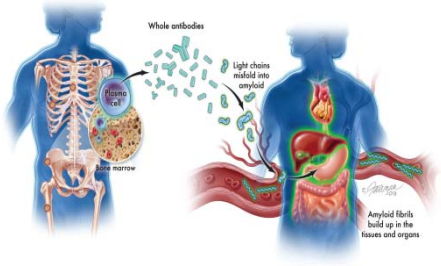
In amyloidosis, plasma cells in the bone marrow produce too many "free light chain" antibodies. These proteins misfold into amyloid, accumulate in the blood, and deposit in many organ systems.

Pathophysiology of Amyloidosis



http://www.amyloidosissupport.com/AmyloidAware_Booklet.pdf

Pathophysiology of Amyloidosis



http://www.amyloidosissupport.com/AmyloidAware_Booklet.pdf

Common Presenting Symptoms of Amyloidosis

Symptoms tend to be vague and include

- Unexplained fatigue
- Unintentional weight loss
- Periorbital purpura
- Edema
- Macroglossia

Rosenzweig & Landau *Journal of Hematology & Oncology* 2011, 4:47

Symptoms (cont'd)

- Abnormal heart rhythm
- Numbness of hands or feet
- Shortness of breath
- Difficulty swallowing
- Weak hand grip

Rosenzweig and Landau *J of Hem & Onc* 2011, 4:47

Revised Prognostic Staging System for Light Chain Amyloidosis

Points
dFLC ≥18 mg/dL
cTnT≥0.025 ng/mL
NT-ProBNP≥1,800 pg/mL

Creates score from 0, 1, 2, and 3 points reflecting Stage I, II, III, and IV

dFLC=difference in free light chains; cTnT= cardiac troponin T
NT-ProBNP=N terminal prohormone of brain natriuretic peptide

Kumar et al *J Clin Oncology* 2012; 30(9) 989-995

Diagnosis of Primary Amyloidosis

Amyloidosis should be suspected when a patient presents with:

- Renal disease – proteinuria, renal insufficiency, nephrotic syndrome
- Infiltrative cardiomyopathy
- Peripheral neuropathy
- Hepatomegaly
- Pseudo-obstruction of the bowel
- Multiple Myeloma – 10-15% of MM patients have amyloidosis

McGowan, N *Dim of Crit Care Nrsing* 2006, 25 (4) 162-165

Diagnostic Screening Tests

- Once considered, the evaluation for amyloidosis includes testing to identify an underlying plasma cell disorder
  - Serum and Urine protein electrophoresis
  - Immunofixation
  - Serum Free Light Chain Assay
  - Bone Marrow Aspirate/Biopsy

Rosenzweig and Landau *Journal of Hem & Onc* 2011, 4: 47

Diagnostic Screening Tests (cont'd)

- Cardiac – EKG and echocardiogram
- Renal – 24 hr urine total protein assessment
- GI – abdominal ultrasound
- NS – nerve conduction studies

Rosenzweig and Landau *Journal of Hem & Onc* 2011, 4:47

Diagnostic Confirmation of Amyloidosis

Tissue sampling is required!

- Demonstrate the presence of congophilic amyloid deposits ("Congo Red positive") OR
- Fibrils that are 7-10 nm in diameter by Electron Microscopy

Rosenzweig and Landau *J of Hem & Onc* 2011, 4:47

Diagnostic Confirmation of Amyloidosis (cont'd)

- In some patients, amyloid deposition will be identified on bone marrow biopsy or by fat pad aspirate (85% of patients)
- But amyloid can be present when both are negative! **Direct biopsy** of involved organ should be performed if index of suspicion is high

Rosenzweig and Landau *J of Hem & Onc* 2011, 4:47

AL Amyloidosis

The diagnosis of systemic amyloidosis requires the presence of all of the following:

- Positive amyloid staining by Congo Red or EM in any tissue
- Evidence that amyloid is light chain related by direct examination of amyloid by molecular methods

AL Amyloidosis (cont'd)

- Presence of amyloid-related systemic syndrome (renal, heart, GI, NS)
- Evidence of a monoclonal plasma cell proliferative disorder [serum or urine M protein; abnormal free light chain ratio; clonal plasma cells identified in bone marrow]

Chaulagain and Comenzo *Curr Hematol Malig Rep* 2013, 8: 291-298

Treatment

The source of the amyloid light chains is a clone of plasma cells histologically identical to those seen in multiple myeloma

↓

Treatments for amyloidosis have been derived from those studied for the treament of multiple myeloma

Treatment

This condition is treated the same way as multiple myeloma would be approached:

- Dexamethasone
- Chemotherapy (including alkylating agents, proteasome inhibitors and immunomodulatory agents)
- High dose therapy followed by ASCT

ASCT=autologous stem cell transplant

Factors that influence approach to treatment

- Age
- Performance Status
- Bone Marrow Reserve
- Renal Function
- Pre-existing Toxicities (peripheral neuropathy, cardiac disease, VTE's)

VTE=venous thromboembolism

Treatment Goal

Eradicate the plasma cell clone to achieve a Complete Response (CR) or a Very Good Partial Response (VGPR) for meaningful reversal of organ dysfunction and for prolonged survival

Hematologic Response Criteria in Amyloidosis

Response	Criteria
CR	Negative serum and urine IFE, normal FLC levels and ratio
VGPR	Reduction of dFLC to <40 mg/L
PR	>50% reduction in the dFLC
No response	Less than a partial response

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Treatment Strategies

Bortezomib based therapy
(bortezomib/cyclophosphamide/dexamethasone or CyBorD)

- High response rates – rapid reduction of free light chain levels
- Favorable cardiac toxicity profile
- Minimal toxicity
- Ease of administration

Treatment Approach in Amyloidosis

Low-Risk (standard risk) patients

- Risk-adapted SCT with bortezomib/dexamethasone consolidation (200, 140, and 100 mg/m^2 of MEL)

SCT = stem cell transplant; MEL = melphalan

Treatment Approach in Amyloidosis

Intermediate-Risk patients (not high risk, not low risk)

- CyBorD or MDex (oral mel/dex)
- Patients who are initially ineligible for ASCT may become eligible if they respond to initial therapy
- Clinical trials

Treatment Approach in Amyloidosis

High-Risk patients [Advanced Cardiac (high risk stage III) or 3 organs involved)

- CyBorD or Mel
- Clinical Trials

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Eligibility Criteria and Schema for risk-adapted Melphalan and SCT

- Age <71 years
- ECOG performance status 0 to 2
- Serum Bilirubin ≤2 mg/dL
- Pulmonary diffusion capacity ≥50% predicted (adjusted)
- Left ventricular ejection fraction≥45%
- NYHA Class ≤2b
- No symptomatic cardiac arrhythmia or syncope within 60 days
- Systolic blood pressure ≥95 mm Hg supine

Chaulagain and Comenzo *Curr Hematol Malig Rep* 2013 8, 291-298

Eligibility Criteria and Schema for risk-adapted Melphalan and SCT

- MEL 200: For patients who are <60 yrs old with no cardiac or renal compromise
- MEL 140: For patients who are 61-70 yrs old with no cardiac or renal compromise; for patients who are <60 yrs old with cardiac involvement or renal compromise
- MEL 100: For patients who are 61-70 yrs old with cardiac involvement or renal compromise

Chaulagain and Comenzo *Curr Hematol Malig Rep* 2013 8, 291-298

Transplant Eligibility Criteria

Only 20% of the patients are eligible for stem cell transplant!

Gertz et al *Am J Hematol* 2013; 88: 416-425

Treatment Related Mortality

- Average TRM in four single center studies is 21% but has been reported as high as 39%.
- Patients with cardiac involvement and autonomic dysfunction are particularly susceptible to fluid shifts and hypotension and should be monitored closely during all phases of treatment including mobilization/collection

Gertz and Zeldenrust *Curr Hematol Malig Rep* 2009, 4: 91-98

Treatment Related Mortality

- Cardiac amyloid patients can experience critical arrhythmias or sudden death during stem cell infusion presumably related to the toxicity of the DMSO preservative
  - Wash cells prior to infusion?

Rosenzweig and Landau *J of Hem & Onc* 2011, 4:47

ASCT Results

Two large studies from experienced centers confirmed the utility of high dose melphalan/stem cell transplant as a treatment for amyloidosis

ASCT Results

Boston University

- 312 patients with amyloidosis were treated with HDM/SCT at 200 mg/m^2 or 140 mg/m^2 based on age and cardiac status
- TRM was reduced to 14%
- Median survival for those who achieved CR was >10 years compared to 50 months for those who did not achieve a CR

HDM/SCT=high dose melphalan/stem cell transplant; TRM=treatment-related mortality; CR=complete response

Sanchorawala et al *Blood* 2007, 110 3561-3563

ASCT Results

Mayo Clinic

- 434 patients with amyloidosis were treated with HDM/SCT over 14 years
- Hematologic response was seen in 76% of patients including 39% who achieved a CR
- Treatment-related mortality was 10%
- Median survival was not yet reached for those who achieved a CR, compared to 107 months for those with PR and 32 months for those with no response

Gertz, et al *Leuk Lymphoma* 2010, 51: 2181-2187

ASCT Results

The strongest predictor of outcome is the hematologic response with those patients achieving a CR having the best outcome

Symptom Management and Supportive Care

- Heart Failure – diuretic therapy
- Cardiac conduction abnormalities – pacemaker insertion
- Renal involvement – dialysis
- Gastric paresis – drugs that increase GI motility
- Postural hypotension – instructing patient to rise slowly from a seated or lying position

Prognosis

- Varies depending on the extent of organ involvement
- The most powerful prognostic factor is the involvement of the cardiac system and individuals with a diagnosis of congestive heart failure have the poorest prognosis

Amyloidosis Points to Remember

- Be alert to signs and symptoms that may suggest a diagnosis of amyloidosis
- Be certain of diagnosis!
- Therapeutic options are based on clinical presentation and prognosis
- Assess for hematologic response!
- ALWAYS encourage patients to consider participation in clinical trials

QUESTIONS?

THANK YOU