AL Amyloidosis & Stem Cell Transplant

Tracy Jalbuena MD

PenBay Medical Center

Clinical Conference

June 3, 2014

Objectives

- Gain better understanding of AL Amyloidosis
  - Its place in broader context of “amyloidosis”
  - Pathogenesis
  - Presentation
  - Natural course
- Appreciate the difficulty and importance of timely diagnosis
  - Less organ damage
  - More treatment options with substantially improved outcomes
- Better understanding of current process of autologous stem cell transplant

Case

- 40 yo otherwise healthy woman
  - Mild fatigue and joint stiffness for 3 months
  - Two weeks of foamy urine
  - Few episodes of unexplained pre-syncope
  - Sudden onset of 2+ pitting edema lower extremities
- Notable labs
  - Twenty-four hour urine protein 6 grams, albumin 2.4 = nephrotic
  - Serum free lambda light chains 20, kappa chains 0.2, k/l ratio 0.014
  - Serum immunofixation monoclonal IgA lambda
  - Urine immunofixation monoclonal IgA lambda

Case

- Images
  - Renal ultrasound, CXR, CT chest/ abdomen/ pelvis all normal
- Bone marrow biopsy
  - Monoclonal lambda light chain restriction, 5% plasma cells (not MM)
- Renal biopsy
  - Apple green birefringence by Congo red staining using crossed polarized light pathognomonic for AL amyloidosis

Case is me

Ulterior motive

- Educate my peers to encourage early diagnosis of others with AL amyloidosis

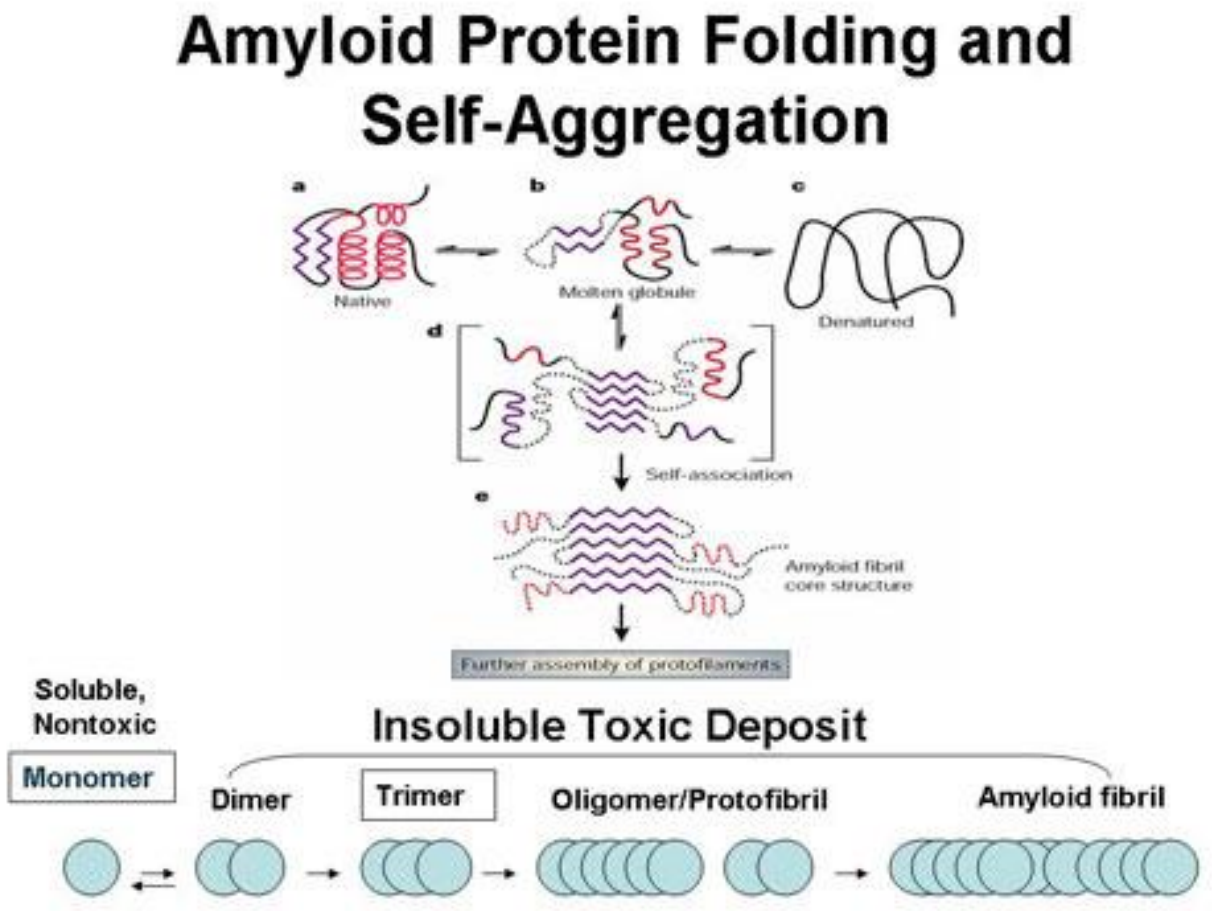
What the heck is “amyloidosis” anyway?

- Folding pattern under the microscope
  - “Starch-like”
  - In 1854 Rudolf Virchow used this term to describe abnormal extracellular material seen in the liver during autopsy
  - Instead of normal alpha-helical pattern, the protein midfolds into a beta-pleated sheet
- Over 25 different precursor proteins can lead to amyloid folding pattern
  - Depending on the precursor protein, deposition presents with very different symptoms, diagnosis and prognosis
  - They need different treatment

They are actually different disease processes

http://emedicine.medscape.com/article/1093258-overview, Gertz 2013

Amyloid protein folding



http://emedicine.medscape.com/article/1093258-overview

Naming system

- Prefix “A” for amyloid
- Followed by an abbreviation for the precursor protein
  - Example AL amyloidosis refers to “Light chain” amyloidosis

Naming

Type	Abbreviation	Precursor protein	Site of synthesis	Symptoms	Treatment
Light chain	AL	Monoclonal light chain	Bone marrow plasma cell	Renal, cardiac, nervous, GI	Chemotherapy, stem cell tx, organ tx
Senile systemic	SSA (ATTR – wild type)	Wild type transthyretin	Liver	Cardiac, carpel tunnel syndrome	Supportive, clinical trials
Hereditary transthyretin	ATTR – mutation	Greater than 100 variants	Liver	PNS/ANS, cardiac, vitreous	Liver transplant
Systemic AA	SAA	Serum amyloid A	Liver	Renal, GI, liver	Suppression of inflammatory disorder
Fibrinogen	Afib	Fibrinogen alpha chain	Liver	Renal, liver	Dialysis, organ tx
Apolipoprotein A1	AApoA1	Apolipoprotein	Liver, intestine	Renal, liver, cardiac, larynx	Organ tx, supportive

Mahmood, 2014

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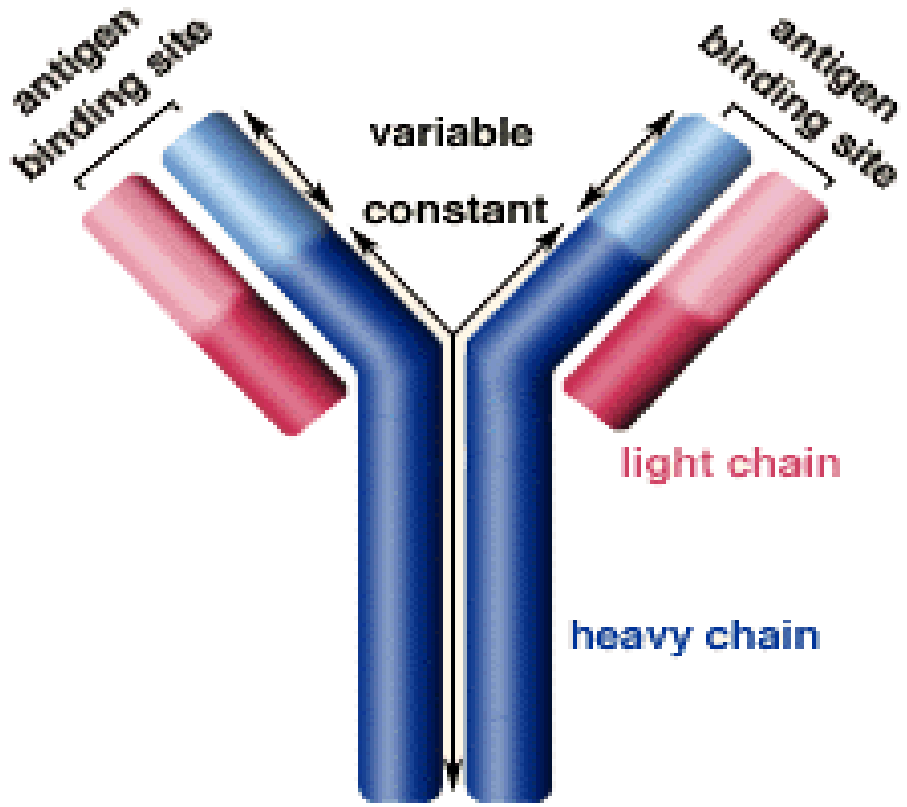
Mahmood, 2014

Definition of AL amyloidosis

- "Immunoglobulin (Ig) light chain amyloidosis is a clonal, nonproliferative plasma cell disorder in which fragments of Ig light chain are deposited in tissues"
- From plasma cells in the bone marrow
  - Mechanistically AL Amyloidosis has a great deal in common with multiple myeloma, as they share dysfunction of the same cell type
    - Almost all the successful treatments so far have been borrowed from multiple myeloma practice
    - 15% of patients with myeloma also have symptomatic AL amyloidosis
      - Worse prognosis than either MM or AL alone

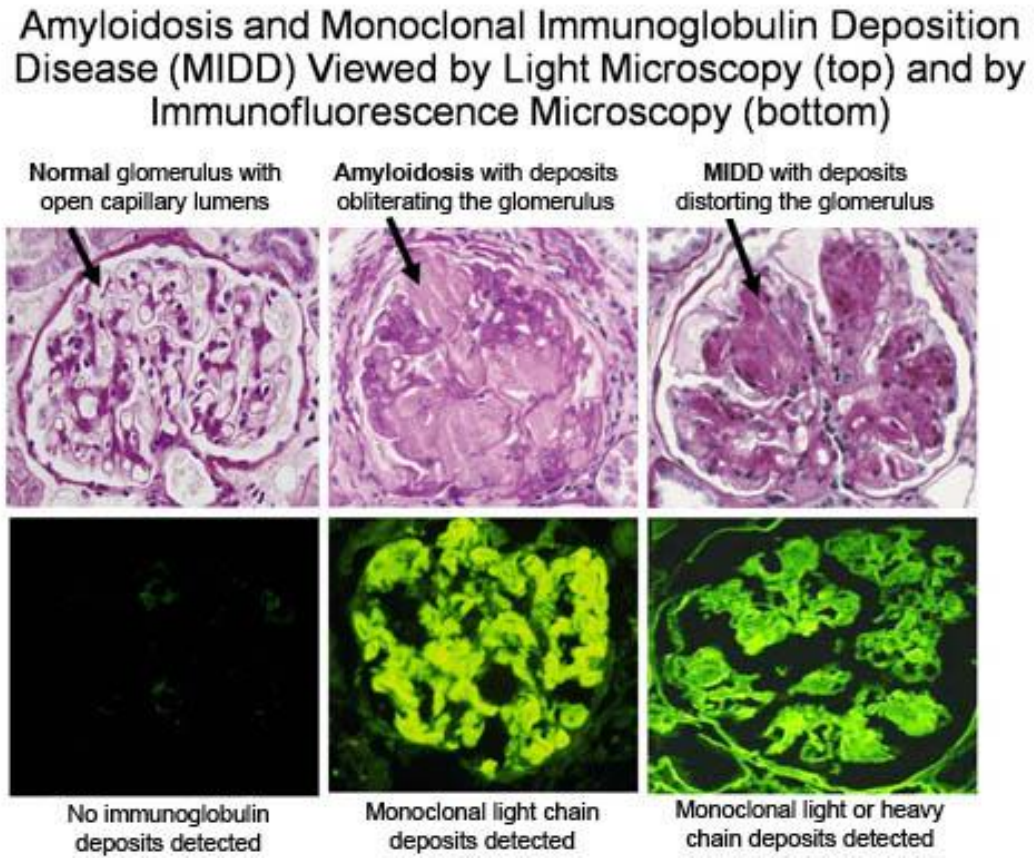
Gertz, 2013; Mahmood, 2013

Light chains



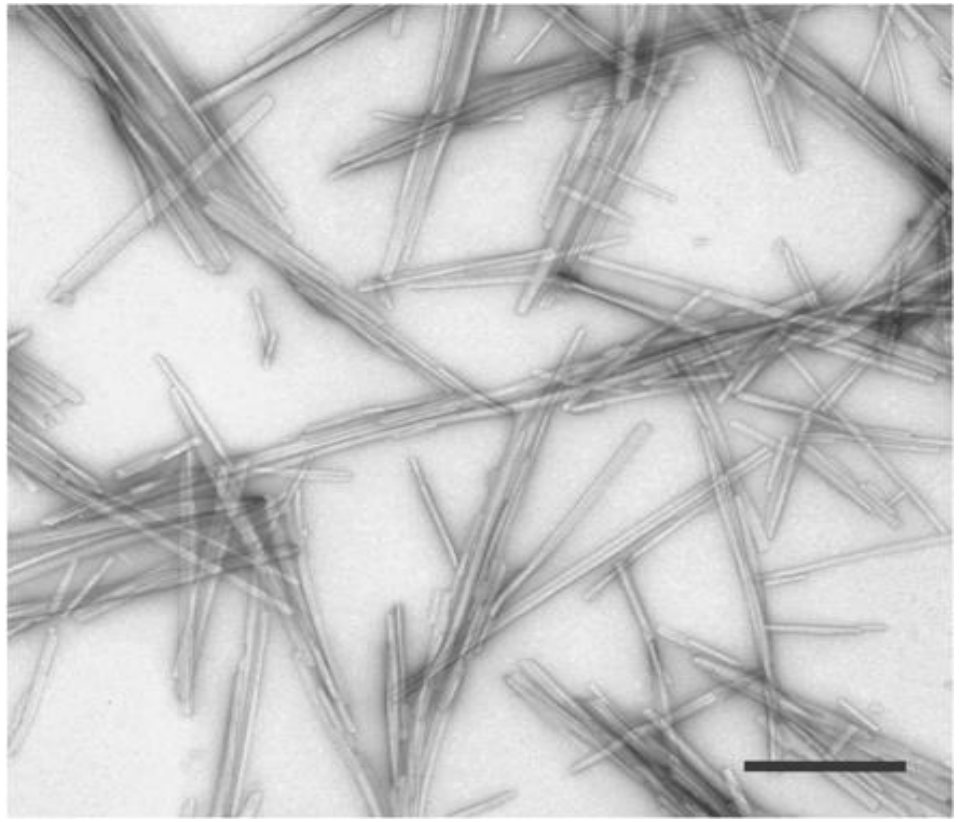
http://www.biology.arizona.edu/immunology/tutorials/immunology/graphics/antibody98.gif

Light microscopy appearance



http://www.unckidneycenter.org/images/amyloid.jpg

Electron microscope appearance



http://www.pnas.org/content/99/26/16748/F2.large.jpg

AL Amyloidosis

- Former name was “primary amyloidosis”
- Most commonly diagnosed type of amyloidosis
  - Rare, with an incidence of 8 per million persons per year
  - 1275-3200 new cases annually in the US
  - 1/5 as common as multiple myeloma
  - About the same incidence as Hodgkin lymphoma or chronic myelogenous leukemia
  - Almost surely under-diagnosed
- Demographics
  - Age – Mean age of onset is 65
  - Sex – Slight male dominance
  - Race – No racial predilection

Comenzo and Gertz, 2002, Sanchorawala, 2012; http://emedicine.medscape.com/article/1093258-overview#a0199

Most common symptoms

- Fatigue
- Weight loss
- Paresthesias
- Hoarseness
- Edema
- Dyspnea
- Carpal tunnel syndrome
- Mucocutaneous lesions
- Hepatomegaly
- Cardiac dysrrhythmias
- Alternating constipation and diarrhea
- Orthostasis
- Bleeding tendency
- Frothy urine

http://emedicine.medscape.com/article/1093258-overview, Mahmood, 2014

Common sites of deposition

- Kidney – 70-100% of AL patients
  - Nephrotic syndrome
    - >3 grams/ 24 hours proteinuria, edema and hypoalbuminemia
- Heart – 50-70%
  - Unexplained restrictive cardiomyopathy
  - Arrhythmias
- Liver – 17%
  - Hepatomegaly without etoh abuse
- Peripheral and autonomic nervous system – 15%
  - Neuropathy and orthostasis
- GI – 10%
  - Abdominal pain

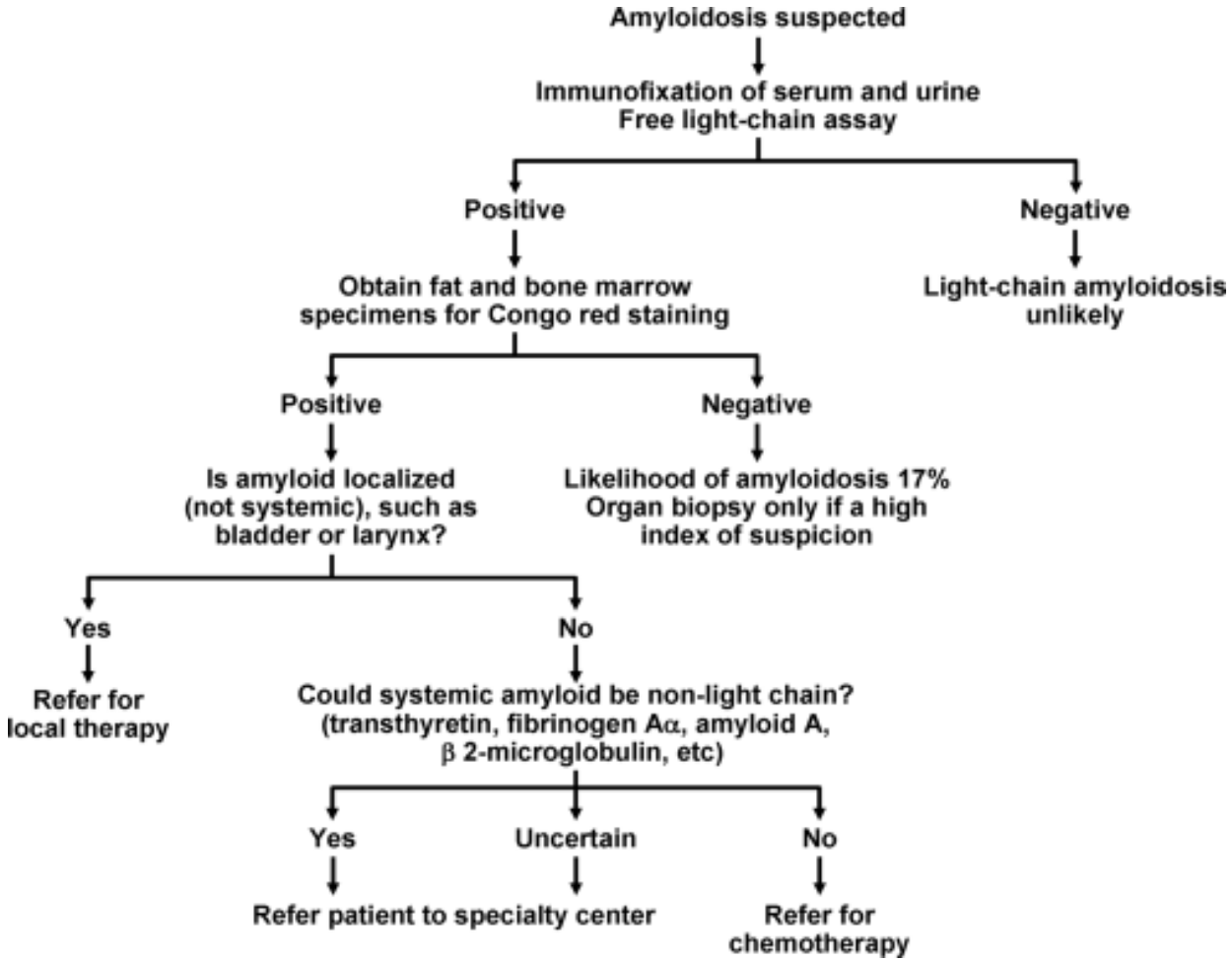
Wechalekar, 2011, Merlini, 2013

Diagnosis

- Peri-orbital ecchymosis and macroglossia are pathognomonic
  - Only occur in 1/3 cases
- CNS is the only unaffected organ
- Diagnosis is often delayed because the symptoms are vague, systemic and mimic more common diseases
- Monoclonal gammopathy (MGUS) or multiple myeloma often precede the diagnosis of AL amyloidosis
  - Patients with MGUS should have regular screening of troponin, BNP and urine for protein several times a year, even while asymptomatic
  - If abnormalities in these tests are found, you should proceed to tissue biopsy

Mahmood, 2014

Diagnosis



Gertz, 2013

Mainstays of diagnosis

- Serum immunofixation electorphoresis
- Urine immunofixation electrophroesis
- Serum free light chains
- Bone marrow biopsy
- Peri-umbilical fat pad biopsy
- Affected organ biopsy

http://emedicine.medscape.com/article/1093258-overview

Prognosis of AL amyloidosis

- Progressive and rapidly fatal if untreated, usually from cardiac dysfunction
- In 1975, Kyle reported chemotherapy was introduced in 1972 using melphalan and prednisone
  - Only a minority responded and median survival was 12-18 months
- In 2002, Comenzo and Gertz reported
  - Median survival from time of diagnosis was 13.2 months
  - Those with CHF had median survival of 4 months
  - Less than 5% of all patients with AL amyloidosis survived 10 years
  - Worse survival than multiple myeloma

Gertz, 2013; Kyle 1975; Comenzo and Gertz, 2002

Prognosis

- Cardiac involvement is still highly prognostic
  - Elevation of troponin and/ or BNP highly prognostic, more prognostic than echocardiogram findings
- Rapid advancements in treatment with multiple clinical trials ongoing
- Current prognosis with
  - Early diagnosis
  - Favorable patient characteristics
  - Early and most aggressive treatment…
  - Now exceeds 12 years, and median survival has not yet been reached
  - Current cohort is the first to reach this survival and is still under study

Sanchorawala, 2013; Gertz, 2013

Treatment

- Send patient to a center of excellence
  - AL Amyloidosis is rare and fatal
  - Treatments are increasingly successful
  - Treatments are very involved and risky
- There are two truly top-notch centers of excellence in the US
  - Boston Medical Center
    - We are lucky!
  - Mayo clinics in Rochester, MN
  - There are other up-and-coming institutions
    - Most of their staff were trained at either Boston or Mayo

Boston Medical Center
A multidisciplinary approach

- Hematology/ oncology
- Cardiology
- Blood bank
- Nephrology
- Pulmonology
- Neurology
- Psychiatry
- Social work
- Research/ clinical trials
- Rheumatology
- Pathology
- Gastroenterology

Boston Medical Center Amyloidosis Clinic

http://www.bmc.org/Images/BMC-moakley-cancer-center-mh.jpg

Boston Medical Center Amyloidosis Clinic

http://www.bmc.org/Images/BMC-moakley-cancer-center-mh.jpg

Three approaches to treatment

- Stop production of faulty light chains/ destroy plasma cell clone
  - Most active area/ most options
  - Numerous active clinical trials ongoing
  - Similar to multiple myeloma approach
    - Data suggests that the AL clone is more susceptible to chemotherapy than the MM clone
    - Chemotherapy with steroids, alkylators and/ or immune modulators
    - Autologous stem cell transplant
- Stop misfolding of light chains
  - I didn't find much about this approach
- Facilitate removal of amyloid fibrils from tissues
  - Active clinical trials ongoing - doxycycline

Gertz, 2013; Merlini, 2013

Three approaches to treatment

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Gertz, 2013; Merlini, 2013

Autologous stem cell transplantation

- High dose chemotherapy to destroy plasma cell clone, followed by patient's own stem cells for "rescue" of bone marrow
- Historically, treatment related mortality has been as high as 40%
- Better patient selection has improved current treatment mortality to 5-7%
- Only 15-20% of newly diagnosed people with AL are candidates for SCT
  - Troponin T < 0.06
  - NT-proBNP < 5000
  - Age < 65
  - Performance status 0-2
  - EF > 45%
  - Systolic BP > 90
  - CO Diffusion capacity > 50%

Early diagnosis is key!

Merlini, 2013; Gertz, 2013; Sanchorawala, 2013

Getting patients to ASCT

- Early diagnosis before amyloid deposits have destroyed organs
- Early referral to center of excellence
- Previous exposure to alkylating agents (ie. Melphalan) impairs hematopoietic stem cell collection
- Some patients who are not candidates for SCT can be treated with stem cell-sparing chemotherapy or even organ transplantation (kidney or heart) and then improve such that they become candidates for SCT

Early diagnosis is key!

Merlini, 2013

Autologous Stem Cell Transplant

- Stem cell mobilization and collection
- High-dose melphalan, an alkylating chemotherapeutic agent
- Re-infusion of stem cells
- Peri-transplant management
- Wait for bone marrow engraftment
- Entire process at BMC usually takes about 8 weeks, if no complications
- BMC tries to do this all outpatient, but only 50% patients can do this
- Must have 24 hour caregiver for the duration

Sanchorawala, 2013

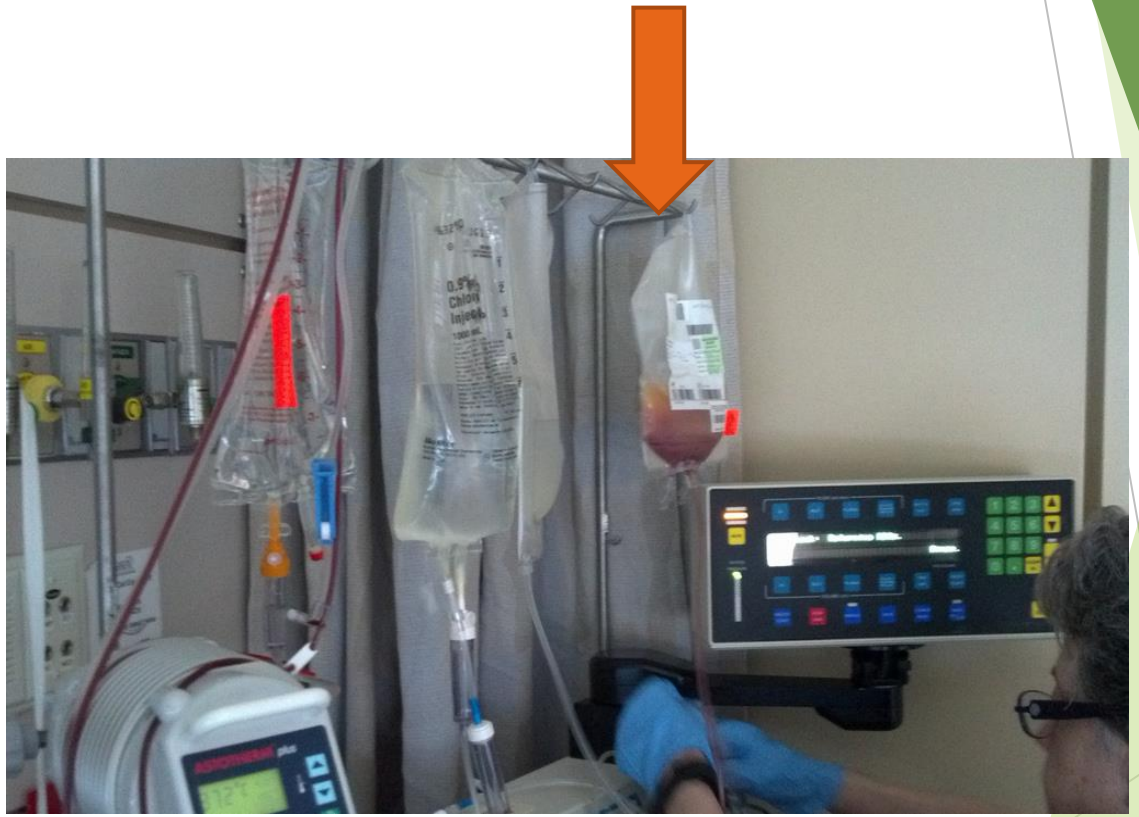
Stem cell mobilization and collection

- Tunneled central line placed
- High dose granulocyte colony-stimulating factor (GCSF, neupogen, filgrastim) IM several days in a row to stimulate stem cell over-production
  - Lots of fluid shifting
  - Unlike in MM patients, there is morbidity and mortality associated with mobilization in AL patients, likely from pre-existing fluid problems
    - Nephrotic syndrome
    - Cardiac dysfunction
  - Cytokine reaction – my WBC at this point was 116
  - Bone pain

Stem cell collection

- Pheresis though central line
- Stem cells are spun down and frozen
- Often more than one collection session is needed
  - 2 x 10^6 of CD34+/kg body weight cells needed at minimum
- Goal is to obtain enough cells for two transplants
- Everything else is immediately reinfused to the patient

Careful with that bag! My stem cells are in there!



Huang, 2014

High-dose melphalan

- Trade name “alkeran”
- Nitrogen mustard alkylating agent
- 200 mg/m2 spread over 2 days
- Modified total dose of 100 mg/m2 based on age and organ function
- Infused over 30 minutes through central line
  - Pack ice in mouth for one hour around infusion
  - Causes vasoconstriction in oral mucus membranes
  - Less mucus membrane exposure to melphalan
  - Significantly reduce or eliminate oral mucositis

Sanchorawala, 2013

Stem cell rescue

- Reinfusion of stem cells one or two days after completion of melphalan
- Through central line
- “Day 0”
- “Bone marrow birthday”
- Peri-transplant time period is through day +100
  - Highest-risk time period
  - Standard time period for purposes of research

Nadir

- Nadir is around Day +12-14
- Profound pancytopenia
  - My low counts were
    - WBC of 0.2 with neutrophil count of 0.00 on Day +8
    - Hemoglobin of 8.8 on Day +11
    - Platelet count of 19 on Day +14
- Slow improvement in counts
- Fatigue
- Nausea, vomiting, diarrhea
- Infection, bleeding
- Pull central line when platelet count goes above 50

Peri-transplant management

- Neutropenic diet
  - Nothing fresh
  - Nothing from the deli
- Daily exam, weight, labs
  - All day in the clinic
- Transfusion of PRBCs and platelets as needed
  - I received platelets
- Fluid management
- Psychiatry
- Daily GCSF until engraftment
- Diflucan
- Levaquin
- Acyclovir
- Compazine
- Ativan
- Dexamethasone
- Zofran
- Safety precautions
  - Nothing sharp or accident-prone
  - No flossing!

Peri-transplant management

- Most patients go back home around Day +20-30
- Weekly labs and visits with PMD
- Weekly email check-in with team in Boston
- Continue acyclovir for one year post-transplant
- 6 and 12 month follow up in Boston, then annually as needed
  - Repeat all the testing
- Re-immunize starting at one year post-transplant
  - Live vaccines must wait until 24 months post-transplant

Response to treatment

- Hematologic response - four criteria by international consensus
  - Maximal hematologic response seen by 6 months or 1 year, at latest
    - Serum free light chains (or ratio between kappa and lambda if renal function impaired)
    - Serum immunofixation
    - Urine immunofixation
    - Bone marrow biopsy
- Organ response measured separately and may take much longer
  - Up to 3 years for maximal cardiac and renal response
  - Complete organ recovery is often not possible

Palladini, 2012; Personal conversations with Sanchorawala V, multiple occasions through 2012-2013

Long term side effects

- Isn't it great that we're talking about *long term* side effects?
- There isn't much data out there, particularly in AL, because the current cohort is the first one to reach *long term*, and they are still under study
- But we do know…
  - Persistent bone marrow suppression
  - Interstitial pneumonia syndrome
  - Cataracts
  - Endocrine dysfunction
  - Infertility
  - Secondary leukemias and other cancers
  - Musculoskeletal disorders
    - Avascular necrosis

Outcomes of ASCT

- In 2013, BMC published their summary experience doing SCTs from 1994-2012
  - 593 SCTs for AL amyloidosis
    - I am in this data set
  - Median age 57 with range of 28-80 (younger median than age of diagnosis)
  - Treatment related mortality (within 100 days) was overall 9%
    - Since 2005, treatment related mortality has improved to 5%
  - 11 deaths during stem cell mobilization
  - Complete response occurred in 40%
    - 44% with higher dose of melphalan
    - 34% with lower dose of melphalan
  - Increase complete response rate to about 65% with tandem ASCT at 6 months if CR not yet reached

Early diagnosis is key!

Sanchorawala, 2013

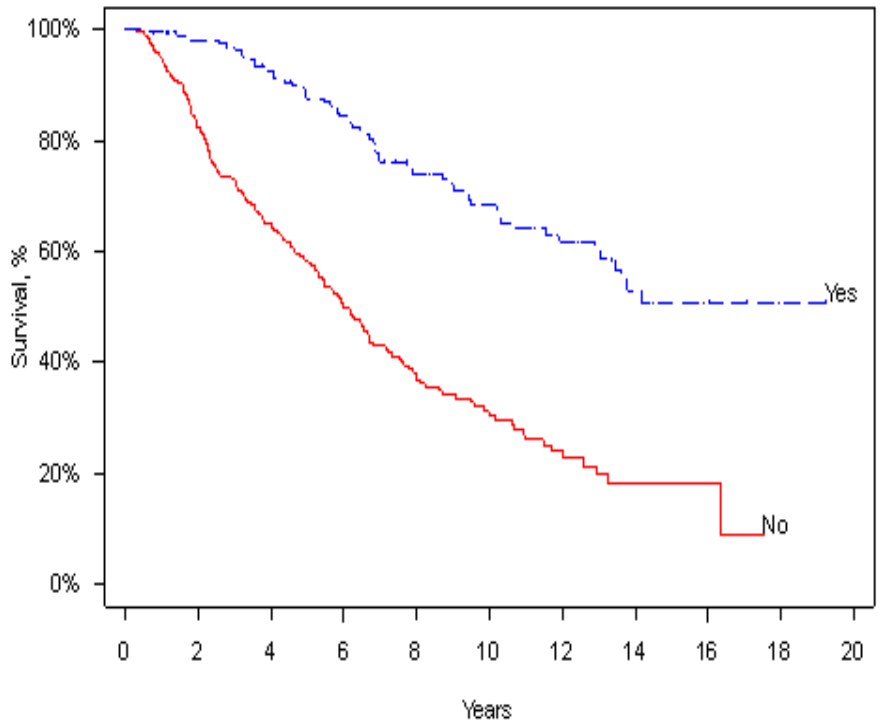
Outcomes of ASCT

- Boston's summary experience
  - Hematologic relapse occurred in 20% of complete responders at median of 3.9 years
  - Median overall survival is 6.7 years
  - Median overall survival for complete responders has not yet been reached, but exceeds 12.4 years
    - Keep in mind that median age of patients undergoing SCT was 57
    - Starting to approach life expectancy
    - What does this mean for someone diagnosed at age 40? Who knows!
  - Boston has a handful of patients still in complete response from one ASCT around 20 years post-transplant

Sanchorawala, 2013

Outcomes of ASCT

Boston's summary experience with ASCT 1994-2012, comparing complete response with less than complete response

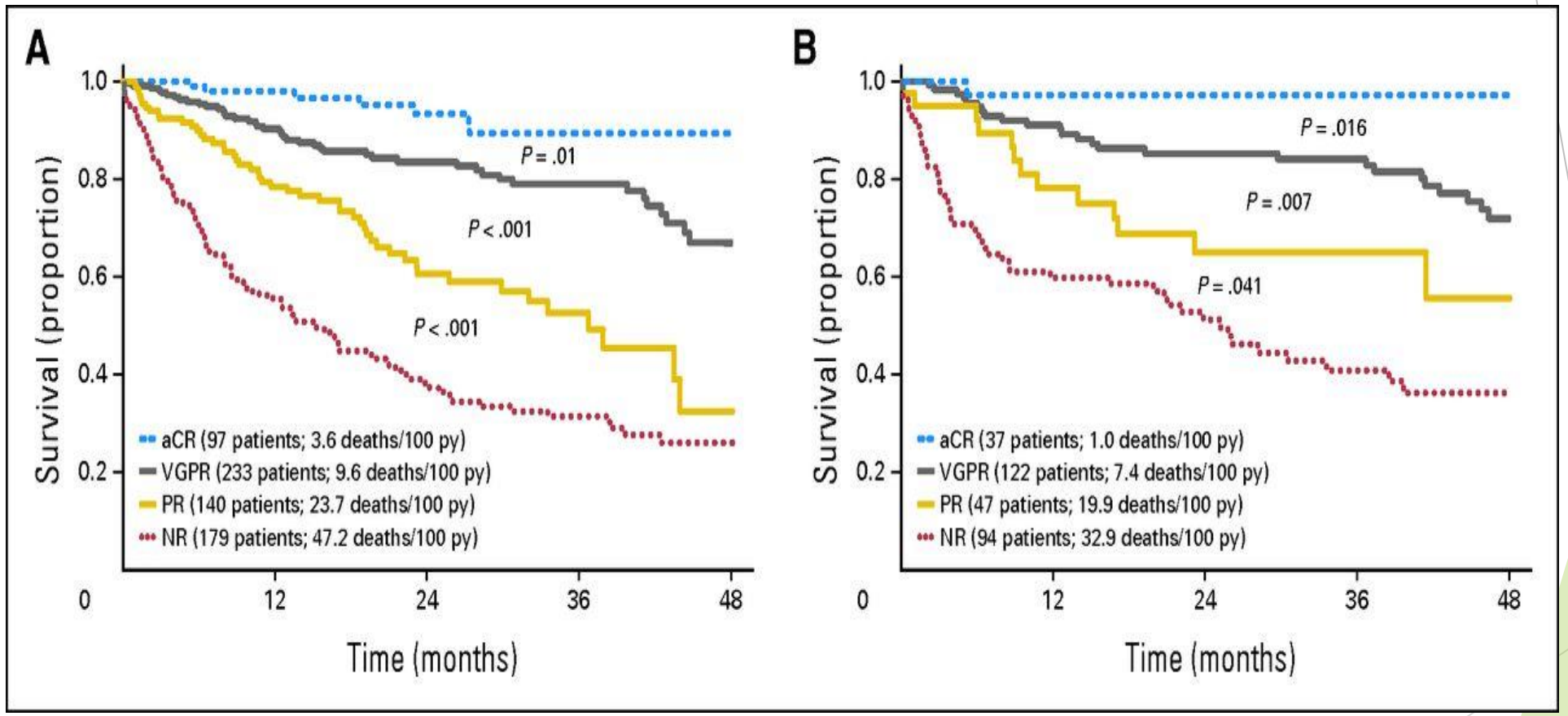


Patients, n

No :	305	231	159	104	59	38	20	7	2	0	0
Yes :	202	189	158	132	93	67	50	26	12	4	0

Sanchorawala, 2014

Outcomes of ASCT



Palladini, 2012

Other therapies

- Duration of response and therefore survival much less than with CR from ASCT
- Lower dose melphalan without stem cell rescue (Alkeran)
- Thalidomide (Thalomid)
- Lenalidomide (Revlimid)
- Pomalidomide (Pomalyst)
- Bortezomib (Velcade)
  - Proteasome inhibitor
  - One of the most promising
  - Used as standard chemotherapy with prednisone
  - Also used as induction therapy just prior to stem cell transplant, with significant increase in the proportion of patients achieving complete response

Huang, 2014; Sanchorawala, 2011

Will AL amyloidosis be curable someday?

- The lead clinical trial nurse at BMC believes AL will be considered curable over the next 10-15 years
- There are so many active clinical trials underway now, several with good results so far
- I encourage you to shift your thinking about AL from a “rare” and “we can’t really do anything about it anyway” diagnosis to “rare” and “should not miss” diagnosis
- Time = relentless organ destruction
- Time = fewer and fewer treatment options

Personal conversation with Anthony Shelton, Clinical Trials RN, Boston Medical Center, June, 2013

Case

- Two cycles of bortezomib followed by ASCT at Boston Medical Center
- Serum free light chains were normalized by bortezomib even prior to ASCT
- Hospitalized twice for fever during ASCT, neither of which turned out to be infection
- Engrafted bone marrow successfully as expected
- **Complete Response** at 6 month follow-up in Boston
- Returned to work gradually starting around 7 months
- This month is two year anniversary, and I continue to have improvement
  - Recovery is very long and arduous
- I went from median prognosis of about 18 months to *at least* 12 years
- Importantly, my quality of life is great
  - Possibly better than yours!
  - I work, I feel good, I take care of my family

Early diagnosis is key

- Early diagnosis is the key to good outcomes

This is why we care

Summary: AL Amyloidosis

- Plasma cell dyscrasia causing light chain aggregation and amyloid fibril deposition in tissues with devastating organ dysfunction
- Symptoms are vague and systemic, but involve most frequently kidneys, heart, liver, nervous system and GI tract
- Diagnosis requires light chain assay, immunofixation, and tissue biopsy
- Prognosis is generally poor, but…
- Treatment is available and rapidly improving
- Autologous stem cell transplant boasts the best evidence for durable hematologic response
- Boston Medical Center has a multidisciplinary center of excellence and is a world leader in all forms of amyloidosis
- Early diagnosis is key to good outcomes

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